PHYSIOLOGY AND PATHOLOGY

OF THE BREAST.

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CONTRIBUTIONS TO THE

PHYSIOLOGY AND PATHOLOGY

OF THE

BREAST

AND ITS LYMPHATIC GLANDS.

BY

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PREFACE.

The investigations described in this volume were undertaken for the Medical Department of the Privy Council by way of inquiring into the causation of malignant tumours. An earlier investigation, on the origin of secondary tumours in the liver, formed the subject of a paper in the Medical Officer's Report for 1874. This paper does not fall within the plan of the present work, and I have not reprinted it. The five chapters on physiological and pathological processes of the breast are reprinted, with additions and corrections, from the Report of 1875, and the chapter on Tumour-Infection of Lymphatic Glands from the Report of 1876. The chapters on development were originally published in the *Journal of Anatomy and Physiology*, Vol. xi., 1876.

The investigations were made during Mr SIMON's term of office, and I enjoyed from time to time the opportunity of conversing with him on the subjects of them. The scope of pathological inquiry which he set before me was of the widest kind, and he strongly encouraged the physiological direction that the work has taken. I desire gratefully to acknowledge his never failing interest in the details of my investigation during its progress, and the assistance that I have derived from his criticisms.

CAMBRIDGE,
28*th Feb.* 1878.

C. C.

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INTRODUCTION.

The breast is one of a group of organs in the body, belonging for the most part to the reproductive system, which have not as yet come to any considerable extent within the scope of the experimental physiology. The breast may be considered to be a sufficiently typical organ of secretion, but the questions relating to the nature of secretion have been tried almost exclusively on other secreting glands, notably on the salivary glands, which come easily within the reach of experiment. But although the breast has been almost neglected by experimental physiologists, and may indeed be viewed as a secreting organ ill-adapted for the application of their method or for the illustration of their problems, yet the circumstances of the breast present an unrivalled opportunity for the study of the process of secretion. The end of experiment may be said to be to vary the circumstances. From the variations so produced, the facts are gained on which to make an induction. As regards the breast, it stands alone among the secreting organs of man's body in presenting to the observer a series of variations which may be called natural or spontaneous in contrast to those that are produced in other glands artificially by experiment. In so far as the circumstances of the breast vary of themselves, under conditions that are well known, the effects upon the secretion have a regularity and certainty which is often wanting to the effects of experiment. Apart from their uniformity, the variations of the mammary secretion are in themselves of the most instructive kind. It is perhaps not altogether superfluous to point out that experiment is nothing more than a means to

an end, and that the scope of physiology includes all generalisations as to function, whether they have been arrived at by experiment or without experiment[1].

The instructive variations in the secretory process of the breast depend on the circumstance that the function is periodically called into play, and periodically subsides. Lactation, properly so called, begins at the birth of the offspring, and, among the various mammals, lasts for a certain number of weeks or months. But the function of the breast is not suddenly called into play at the time of parturition, nor does it suddenly cease at the end of suckling. The function subsides gradually, and when the next pregnancy is established, it returns by still more gradual stages to the full intensity that it possesses at or just after the birth. It is in the stages of gradual subsidence, of still more gradual reawakening, and in the remarkable parallelism between them that one finds the valuable means of generalising upon the mammary secretion. Hand in hand with the subsidence of the function, there goes on an upfolding of the structure, the result of which is visible externally in the diminished size of the organ. The revival of the functional activity is in like manner accompanied by an unfolding of the structure, the outward sign of which is the increasing size and turgescence of the organ from the early months of pregnancy to the time of delivery. The variations in the intensity of the secretory force as measured by its products correspond to changing aspects of the secreting acini. In following the processes of upfolding and unfolding structure, of subsiding and reviving intensity, one is sometimes apt to think that the mysterious dualism of structure and function comes near to being surprised of its secret.

Notwithstanding the attractive nature of the problems here offered for study, the periodical processes of the breast have been hitherto almost entirely undescribed. Langer has indeed referred to them, and in his memoir[2] on the breast, published in 1852, he expresses the intention of afterwards entering more fully into the subject. But in an article[3] on the breast, published in 1870, he

1 "Observation is *finding* a fact, Experiment is *making* one. The worth of the fact depends on what it is in itself, and not on the manner of obtaining it."
Bain's *Logic*.

2 *Denkschriften der Wiener Akademie*, 1852.

3 Stricker's *Handbuch*.

goes no farther than to refer to the upfolding process under the name of the involution of the gland, and to describe briefly and in general terms the resting state of the gland, or the condition in which it remained at the end of involution. I do not find that these questions relating to the breast have been either fully stated or at all worked out by any other author.

The term "involution," used by Langer for the upfolding process, appears to be very suitable, and will be used in the sequel, with the addition of "periodical" to distinguish it from the final atrophy or disappearance of the secreting structure that occurs in women at the climacteric years, as part of the general "sexual involution." If the word "involution" be used for the upfolding process, the correlative term for the unfolding process cannot well be anything but "evolution." Both terms will at least have the advantage of being applied in their literal sense, and the evolution being further defined as "periodical" may perchance escape the danger of being mistaken for any of the other and sometimes lax applications of that word[1].

The first two chapters will contain an account of those two processes of the breast. The third chapter treats of the lymphatic glands near the breast as appendages of the secreting gland. While the chapter on lymphatic glands is an integral part of the investigation on the mammary secretion, it is at the same time an independent contribution to the knowledge of the structure and function of lymphatic glands; and it will be found to contain a comparatively new exposition of their function.

The fourth and fifth chapters contain a new account of the development of the breast, and some considerations on the development of its function. The development of the function of an organ is naturally bound up with the development of its structure; it is the same dualism of structure and function that has been referred to. But the function in its development is as capable of independent treatment as the function in its maturity; and I

[1] Astley Cooper (*Anatomy of the Breast*, London, 1840) applies the term evolution to a group of developmental processes, including the first formation of the gland in the embryo, the changes that it undergoes in both sexes up to puberty, and the completion of its development or expansion in the primipara. He contrasts also the full state of lactation with other states of the gland. (See a reference to one of his observations in the second chapter.)

shall best justify my introduction of it as a separate topic by quoting the conclusion that I have arrived at. The embryonic cells, in order to become the secreting cells of the mammary acini, go through a cycle of changes; and the changes that they undergo are precisely those that the cells of the mature organ undergo in producing their periodical secretion. The function of the breast is therefore said to be a sustained repetition of its development. The first "period" of the breast is its development.

Chapters VI. and VII. contain the application to disease of the physiological principles established in Chapters I. and II. They treat of morbid physiological processes of the breast, and they endeavour to show from the examination of a series of cases that the common and malignant tumours of the breast, as well as some of the rarer forms (Chapter VII.), owe their origin to functional irregularities of the gland. The varieties of cancers of the breast, hard and soft and the like, have necessarily been kept in view; but the tumours are here discussed, not with reference to their subdivision on points of structure, but always with a view to making out the particular departure from the normal process of the gland to which their existence in each case is due. In other words, it is the excitation (*Reiz*) that is chiefly considered. In a former paper[1] I defended the use of the word "cancer" as a general name for all malignant tumours. It is here used in that sense; and it can be so applied with strict propriety to a class of tumours described in the sequel, which from the shape of their cells might be called sarcomata, but which are none the less the product of functional disturbance of the secreting parenchyma.

The last chapter is an application to pathology of the facts arrived at in Chapter III., on the function of lymphatic glands. The lymphatic glands of the breast being viewed as functional appendages of the secreting gland, it is possible to treat their invasion or infection in cases of tumour-disease of that organ as being in a very particular way incidental to the health-relationship subsisting between them. This physiological clue to the infection of mammary lymphatic glands has been made use of, in the latter part of the chapter, to illustrate by resemblance and by contrast the general question of tumour-infection both as re-

[1] "On the Histogenesis of Secondary Tumours in the Liver," in the *Report of the Medical Officer of the Privy Council* for 1874, pp. 95, 96.

gards the primary and secondary tumours of other epithelial organs, and also as regards the primary and secondary tumours of connective-tissue parts.

At the beginning of this preface I contended that it was possible to study the functional processes of a gland so far without the modern aid of experiment. I might now in like manner point to the pathological conclusions of my investigation as showing the utility of a kind of physiology that is neither physiological physics nor physiological chemistry. The cellular pathology is nowhere more triumphant than in the region of tumours, and I believe that for every organ or part of the body that is subject to the tumour-disease—not to speak of other diseased processes—there exists a cellular physiology as distinguished from histology, which will always demand a fair share of attention at the hands of the medical profession. However convenient and however philosophical it may be in modern physiology to ignore the individual elements of the body, and to view them in the abstracted form of a protoplasm upon which forces play or in which chemical changes take place; yet, when we come to the everyday processes of disease, the elements of the body are constantly asserting their individuality, and in the case of tumours they assert it in the most alarming way. It appears to me, therefore, that physiologists owe greater consideration to the cellular unit of the body, and to the spontaneity and self-governing properties of the cell.

PART I.

PHYSIOLOGICAL.

CHAPTER I.

THE PERIODICAL INVOLUTION OF THE BREAST.

It will be convenient to give, at the outset, some account of the mamma in its state of perfect expansion and full secretory activity, not with a view to bringing forward new points, but for the sake of illustrating the successive changes that the organ undergoes. The characteristic appearances of a gland well advanced in involution will next be described. This condition of the organ has been found, in the dog, cat, sheep and rabbit, to fall between the fourth and sixth weeks after lactation has ceased, and it may be taken to be the resting state of the mamma. The entire series of intermediate changes from the end of suckling to the resting state will then be entered on, and this part of the investigation will afford an opportunity for discussing what appears to be a law of the secretion.

During the period of lactation, and for a few days both before and after it, the mamma is found to be a finely lobulated organ, of a pinkish colour, succulent, of uniform consistence, and having generally a greater resemblance to the pancreas than to the salivary glands.

In the dog, cat, and rabbit, the chain of glands extends along each side from the groin to the middle of the thorax; except in one case in the cat (a primipara) the chain of glands has been found to be confluent, forming a single long strip on each side. In the case mentioned as an exception there were found, corresponding to the five teats, five perfectly distinct circular glands with bands of connective tissue stretching between them. In the

general case where the glands are confluent, the same appearance of isolated circular areas is produced by the several sets of ducts (where these are visible) radiating towards each teat.

In the dog, cat, and rabbit there are from four to five teats on each side, in the sheep there are two pairs, a large and a small, and in the guinea-pig there is a single pair. In the animals that have the extended chain of glands, the anterior two-thirds of the chain is flat and thin, being about two inches in width, and a line or more in thickness; towards the inguinal region the gland becomes much narrower and thicker, and tapers to a rounded end at the symphysis pubis. The upper surface of the gland is closely adherent to the skin throughout; the lower surface is separated from the abdominal wall by a thin layer of loose connective tissue in the anterior part of the chain, and in the inguinal region by a cushion of fat of variable thickness. Small bundles of striped muscular fibre are met with at various points in the gland, running in a longitudinal direction. Their occurrence is, however, not uniform, and there is no regularity in their distribution; they have the appearance of being detached bundles of the subjacent muscle which have, during development, become included in the gland substance.

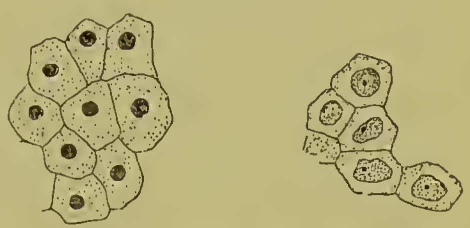
In the minute structure of the fully expanded gland, the following points are to be noted. Each lobulus is composed of a large number of closely packed acini, for the most part of round shape and uniform size, while those at the borders or corners of the lobule may be larger and elongated. The lobules are separated from one another by very thin tracts of loose connective tissue; the acini making up a lobulus are bounded by the encircling blood-vessels and their adventitia. The grouping of the acini round the ducts cannot well be made out in sections of the fully expanded gland. The floor of an acinus in section is covered by a mosaic of polyhedric epithelial cells, usually to the number of 15 or 20, while in the larger elongated acini as many as 30 may be counted. The cells are usually pentagonal or

Fig. 1.

Fully-expanded acinus of the mamma, showing mosaic of polyhedric epithelium. Magnified 300 diameters.

hexagonal, and the corners are sometimes rounded. In each cell there is a central round nucleus which colours brightly with the staining fluid (purple with logwood), and a broad fringe of protoplasm which stains less deeply. The nucleus is on an average not more than one-third of the entire breadth of the cell. Fig. 2 shows variations in the size of the nucleus relative to the surrounding protoplasm. In a profile view of an acinus the epithelium appears as a circlet of oblong cells in which the nucleus at the centre occupies almost the entire thickness of the cell. The mammary epithelial cell may therefore be described as a flattened polyhedric body, with a thickness about one-half of its breadth. The substance of the nucleus is apparently homogeneous, with a deeper line of staining round the margin; a nucleolus is not always prominently seen. The broad fringe of protoplasm is more or less granular or hyaline, varying according to conditions that do not require to be discussed at the present stage. By special methods of preparation the meshwork of the basement membrane may be demonstrated. It is seen to be a regular arrangement of delicate fibres, forming polyhedric spaces in which the epithelial cells are set. It may be added that the best preparations of the perfect mammary epithelium are obtained, not when the animal is in milk, but two or three days before parturition.

FIG. 2.



Mammary epithelium, showing variations in the relative amount of nucleus and cell-substance. Magnified 300 diameters.

Turning now to the description of a gland well advanced in involution, the extent of the changes that constitute the involution process will become at once apparent. The particular case of a bitch killed five weeks after lactation had ceased may be taken as an example. The entire chain of glands is considerably reduced in thickness, and the anterior end of the chain so much so as to be quite membranous. In the thinnest part of the chain, the ducts, which are not to be seen in the state of full expansion, are now visible as large round cord-like structures radiating from the periphery to the nipple. The inguinal portion of the chain now rests on a thick cushion of fat; in certain cases this cushion

has been found to be as much as three-quarters of an inch in thickness, while the gland-tissue formed, as it were, a mere covering drawn over it. The cushion of fat is also observed to contain small lymphatic glands embedded in it. On cutting into the gland thus reduced in thickness, its substance is found to be tough, and to consist of large tracts of not very dense fibrous tissue, interposed between small round or linear areas of the involuted glandular tissue. The latter have the usual colour and the soft or parenchymatous section of glandular substance, and in the plane of section they incline to stand out slightly above the level of the fibrous stroma. In the greatly flattened or spread-out kinds of glands, as in the dog, cat, and rabbit, the longitudinal section has a stratified appearance, from the arrangement of several involuted lobuli in a long narrow strip, with corresponding parallel tracts of connective tissue. In the more compact glands of the sheep and guinea-pig, the islands of glandular tissue are more uniformly scattered over the plane of section. It sometimes happens that the tracts of connective tissue between the lobules are occupied by fat. Where this is the case, the contrast between the true glandular and the other tissue is very marked, and the stratified or mottled appearance more striking. The glandular tissue might be estimated roughly to make up less than one-half of the entire bulk of the organ. The section of the involuted gland shows also numerous large ducts and blood-vessels cut across.

On microscopic examination the ducts and blood-vessels are always conspicuous. In sections of the fully-expanded glands they are seldom encountered; but the great retraction of the glandular substance in the involuted state enables them to become prominent. The fibrous tissue, as has been stated, is sometimes occupied by fat. In most cases, however, the tissue between the lobules is purely fibrillar or coarse fibrous, and the greater or less amount of fat seems to follow the individual peculiarities of the animal. The most striking instance of fat formation occurred in a rabbit. A portion of the mamma, four days after the young were taken away, was found to have the uniform parenchymatous appearance of the fully expanded gland. When the animal was killed ten days later, the glandular tissue was found to be greatly retracted or involuted, and the involuted lobuli or groups of lobuli

to be separated by broad tracts of pure fat-tissue. This rapid development of fat in the rabbit is in accordance with the observations of Toldt[1] and of Czajewicz[2] as regards the rapid disappearance or new formation of the fat-tissue generally in that animal.

The attention is next directed to the minute structure of the gland-tissue proper in the state of involution. The small areas of glandular substance are found grouped with some regularity round the larger ducts. Fig. 3 shows a large central duct, send-

Fig. 3.

From the mamma of a bitch five weeks after the end of lactation. Characteristic appearance of involuted lobules grouped about a duct. Magnified 90 diameters.

ing a branch at its upper end into the centre of a lobule; the other lobules round about it are evidently cut in a plane that does not show the branches of the duct passing into them. The lobule in involution preserves its entirety; that is to say, the acini composing it remain as closely packed together in the involuted state as in the state of full expansion. There is occasionally found a small growth of connective tissue between the

[1] *Sitzungsberichte der Wien. Akad.*, Juli, 1870.

[2] Quoted by Toldt.

separate acini of a lobule; this is best seen in the udder of the ewe. It is sometimes also observed that the more outlying acini of a lobule are detached from the rest by a few fat-cells in cases where fat occurs in the gland. But generally speaking the lobule shrinks up *en masse,* and it is often found that two or three entire lobuli remain closely packed together.

FIG. 4.

Appearance of an involuted lobule with higher magnifying power (300 diameters).

The involuted acini present very definite characters, which have been found to occur with great uniformity. Each acinus appears on section as a rounded space bounded by a continuous thin membrane, which generally colours deeply with the staining fluid. It most commonly appears as if the lobule were made up of a number of independent round spaces, but the infundibular or trefoil-like appearance of several communicating acini can often be seen. The diameter of an involuted acinus is about one-fourth that of the acinus during lactation. The contents of the involuted acinus are the chief point of interest. Instead of the cellular elements being to the number of 15 to 20 or more, as they are seen to be in the floor of a perfect acinus, they number, in the sectional view, on the average half-a-dozen; and instead of forming a mosaic of large polyhedric cells of which the central nucleus is not more than one-third of the whole breadth of the cell, they are nothing else than a somewhat irregular heap of naked nuclei, with no fringe of protoplasm round them, and in size little if at all larger than the nucleus alone of the perfect epithelium. The cellular bodies of the involuted or resting state are however not all of them round or elliptical; a certain proportion of them are more oblong, others are crescentic or more or less triangular. They colour with the staining fluid the same as nuclei; the more round or oval forms show a nucleolus.

The involuted acinus is to be regarded as a spherical space more or less completely filled with a number of nuclear bodies. The elements of the basement membrane are not readily made out. There are now and then seen what appear to be spindle-

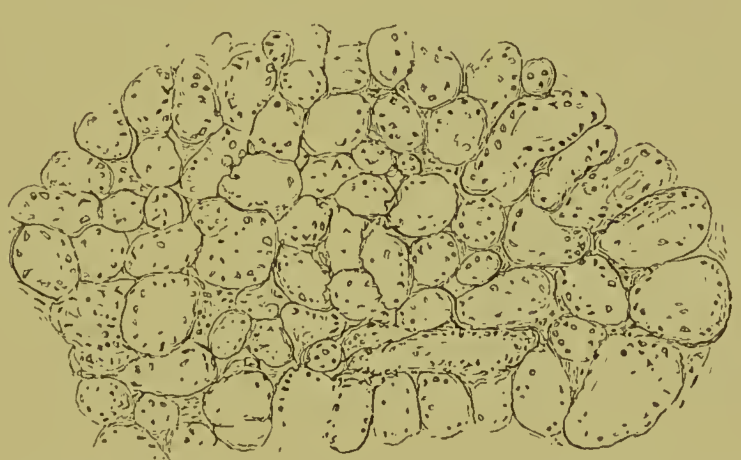
shaped or oblong thickenings in the substance of the limiting membrane; but it is doubtful whether these are not to be classed with the heap of cells within. In like manner there are seen, among the cells in the interior, stellate and other forms which cannot always be distinguished from the crescentic or other irregular forms of cells belonging without doubt to the general intra-acinous group of cells.

Capillary vessels of a relatively large size can be seen branching in various directions among the acini of the lobule; but they are not seen to encircle the individual acini in the same manner as in the state of full expansion.

Having thus far described the fully-expanded state of the secreting structure, and the involuted or resting state of the same, we are now in a position to trace, from the intermediate conditions of the gland, the entire course of the involution process.

The adjoining figure is a low-power view of a lobulus from the mamma of a cat that had suckled its young for sixteen days, and had then been kept apart from them for nine days. When the

FIG. 5.



From the mamma of a cat nine days after lactation. Lobule retaining its full expansion, with a change in its epithelium. Magnified 90 diameters.

animal was killed at the end of that time, the mammary glands were found little if at all diminished in volume, and to have the ordinary prancreas-like structure of the lactation period. The substance was, however, not at all loaded with milk. On microscopic examination, the lobuli, as the figure shows, were found for

the most part to be of the same size as in the state of full development, and the connective tissue separating them was inconsiderable. The acini also were of much the same shape and size as in the secreting gland. But their contents were totally different. While they retained their size and form, their floor, instead of being covered with a mosaic of polyhedric epithelium, presented the following appearances, which were characteristic everywhere of the gland-structure of this animal. It may be stated also that the appearances were the same in various sets of preparations, whether hardened in chromic acid or in methylated spirit, and whether coloured with logwood or carmine. Each acinus had strewn over its floor, or arranged at somewhat wide intervals round its margin, a number of deeply-stained cellular bodies of various shapes. Some of them were round, some more or less cubical, a certain number were of a somewhat thick crescentic shape (hemispherical), and others were triangular. Their size corresponded generally to that of an epithelial nucleus, and their substance coloured uniformly throughout. It was at the same time apparent that the floor or circuit of the acinus was also occupied by a number of delicate ring-like forms of a greyish unstained granular appearance, and that the variously shaped cellular elements were seated on their periphery (Fig. 6). This was most obvious in the case of the crescent-shaped coloured masses, for they completed the circuit of which the thin uncoloured thread formed the larger part. The triangular-shaped bodies were also very significant; they were found situated below the point of contact of two such hoops or rings, a scooped-out side of the triangle forming a part of each circle, and the single triangular body evidently represented the fusion at their opposed surfaces of two independent crescentic bodies.

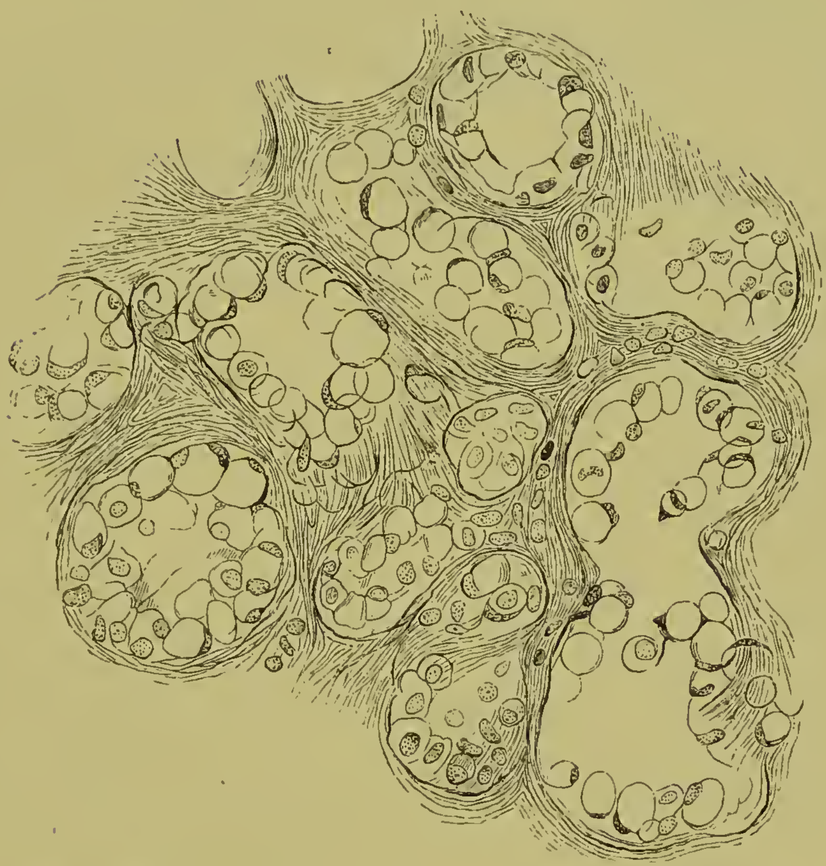
Fig. 6.

The contents of the acini in Fig. 5 under a higher magnifying power (360 diameters).

The interpretation to be given of these appearances will be made less doubtful by describing what is found in a somewhat different preparation of which Fig. 7 is a drawing. This is from the udder of a ewe which was said to have been killed a short time after the cessation of the milk. The acini were generally of a large size, and their contents showed several interesting

modifications of the condition observed in the preceding case. The sections showed more frequently the profile view of the

FIG. 7.



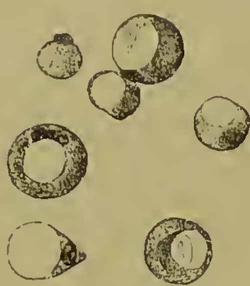
From the udder of a ewe shortly after the end of lactation. Vacuolation of the epithelium *in situ*. Magnified 300 diameters.

epithelium, in which the cells were arranged as a complete circlet adhering round the circumference of the acinus; and many acini showed, in addition to the circlet of epithelium *in situ*, an irregular heap of cells lying free in the lumen of the acinus.

The portion of the gland of which Fig. 7 is an accurate drawing did not show the latter condition, but the group in Fig. 8 are representative forms of the cells that are frequently seen to occupy the lumen of the acini in other parts of the preparation. The cells *in situ* are vacuolated cells, with the usual thin and for the most part uncoloured hoop or ring of the vacuole, and the deeply stained peripheral mass. The most definite and unmistakeable form of vacuolation is the signet-ring type, which

occurs over and over again in these preparations. Another not uncommon appearance, which would be ambiguous if taken by itself, is where the coloured or nuclear element of the epithelium is, to use the current expression, set free from the parent cell, which is evidently not destined to survive the setting free of the young cell. In those cases the definite boundary of a vacuole and the excentric position of the coloured mass are not apparent, but the phenomenon is one of the same class. In the groups of cells that are found lying free in the lumen of an acinus, the process of excavation or vacuolation of the cell substance is very obvious. The cells are true hollow spheres, showing the entire cavity, and not merely a section of it. Individual instances may be observed among them in which the cell substance is seen to be simply granular and not vacuolated; but in these also the excentric position of the nucleus can be seen. Others, again, of the group are round granular cells, showing neither nucleus nor vacuole. The size of the various cells, whether of those *in situ* or of those in the free cavity of the acini, will be found to correspond on the whole to the size of the perfect mammary epithelium. If the latter were to become globular and to retain their greatest breadth as their diameter, they would have much the same size as the cells now described.

Fig. 8.



Characteristic appearance of cells occupying the cavities of the acini in an early stage of involution. (From the same case as Fig. 7.) Magnified 300 diameters.

There is thus a gradual transition from the perfect mammary epithelium to the forms that characterise the various stages of the involution process. The two cases that have been described and figured are merely good examples of what is found uniformly to occur. The various characteristic appearances in the epithelium are found to occur throughout a period extending to the fourth or sixth week after lactation. If the cellular elements of the acini in Fig. 6 are again referred to, it will be seen that they are not unlike those described for the completely involuted or resting state. The remaining steps of the involution process as regards the acini may in the meantime be supposed to be the contraction of the space of the acini as figured in Fig. 5, and the retention of a certain part of the cells within them. This account will have to be

supplemented later by some important particulars, but it is convenient to leave it at present as it stands.

The ultimate contraction of the circuit of the acini evidently depends on the collapse or yielding of the vessels that encompass it, and make up the most substantial part of its framework. This, again, is related to the diminished supply of blood during the subsidence of the secretion. As the acini contract they preserve, as has been already said, the unity of the lobule, and it is not between the several acini but between the several lobules, and sometimes groups of lobules, that a space is set free. There is, as has been explained, an absolute shrinking up of the whole gland. But there is also an increase of the connective tissue between the lobules, which goes on *pari passu* with the retraction of the latter; and where there is no actual increase in the quantity of the interlobular tissue, there is a formation of fat in it. The production of young fat-cells among the interlobular fibrillar tissue may be clearly seen. The increase of the cushion of fat beneath the gland has already been mentioned. The economy of this process of fat-production is obvious. By means of the submammary layer of fat, the contour of the body is preserved, and by means of the fat within the gland the necessary intervals between such permanent structures as the large ducts and blood-vessels are filled up. In both situations there is the greatest amount of space occupied by employing the least number of cellular elements.

Such then is the process of involution in the epithelium and in the other tissues of the mamma in so far as its morphology is concerned, or in so far as the simple description of its various phases can carry us. It remains now to enter on a discussion of the physiological significance of the process.

The epithelium of a mammary acinus examined while the animal is in milk is found to be coarsely granular; but it is not always easy to find good examples of the perfect epithelial cells where the formation of milk is actively going on. The character of the epithelium, as has been already stated, can be best seen in the gland shortly before parturition. It is generally admitted that the milk is formed at the expense of individual epithelial cells, and that the epithelial cell perishes in being transformed into the fluid of the secretion. There is, indeed, an observation of Stricker's,

which is taken to show[1] that the same epithelial cell may yield successive contributions to the secretion. He observed that colostrum cells swimming in fresh milk gave out fat globules, while they retained their form. The observation as far as concerns colostrum cells is no doubt correct; but it is at the same time clear that the same colostrum cells could not return to their place on the wall of the acinus and resume their function of milk-production. Whatever properties they may have had as free cells, their career as epithelial cells was over. The cells in Fig. 8 are identical with colostrum cells, and it has been already mentioned that they occurred in the lumen of acini, the walls of which were also covered with a set of epithelium, the colostrum cells being in fact the predecessors of those that then had the epithelial position. It may, indeed, be taken as settled that the secretion is produced by the transformation of the substance of epithelial cells and the necessary destruction of the cells[2]. This process means no less than the constant renewal of the epithelium; and here we are met with a difficulty. The mammary epithelium is an epithelium of one layer, and there is no doubt a difficulty in representing to the mind the double process, the secretory process and the formative process on which it depends, as taking place in an epithelium of one layer. The type of the secretion is, however, the same as in the sebaceous glands, and that of the latter may be compared to the desquamation of the neighbouring epidermis. Now, in the case of the skin, the numerous layers of cells enable the process to be clearly seen. In the lowest layers there is a multiplication of cells by the ordinary hyperplastic process of division; a layer of cells that have begun their career in this manner as formative or-

[1] Langer, *Stricker's Handbuch*, p. 632.

[2] The following extract from an article by Professor Voit expresses the now accepted view of the formation of milk, and illustrates that kind of secretion by contrast with another:

"The cells or cell-derivatives of many parts of the body effect, for an indefinite time and without themselves perishing, the most active decompositions of the substances passing through them; such, for instance, are those of the liver, of muscle, of the central nervous organs. The cells of the blood, the epidermic and epithelial cells, and also those of the breast, are however made subject to change; and for the latter the theory of secretion remains true that was stated generally by Goodsir and Meckel, according to which the dissolved gland-cells represent the secretion. Milk is not a product of the activity of cells of the gland, but it is the actual cell-mass become fluid."—(*Zeitschrift für Biologie*, 1869, p. 140.)

plastic cells come in their turn to the surface, and undergo the horny transformation, after which they are cast off. There is here no special class of cells which are set apart for formative activity; the same cells are at one time in a formative stage and at another time in their functional stage, and the many layers of the cells enable us to see the two incidents of their life apart. The difference in the mamma is that there is visibly present no new generation of cells in readiness to take the place of those that are cast off, but that difference entirely depends on the epithelium being an epithelium of one layer. The same cycle which is, as it were, unrolled in the *rete mucosum* and epidermis, is implicitly present in the activity of the mammary epithelium. With this explanation, it will be convenient to separate the notions of the formative and of the functional activity of the epithelial cells, the latter constantly presupposing the former.

The secretion then may be said to be produced by a transformation of the substance of successive generations of epithelial cells, and in the state of full activity that transformation of the substance is so complete that it may be called a deliquescence.

The process in the cells presents in fact no morphological characters whatever. But when the secretory activity of the gland is weakened, as in the subsidence of the function during involution, the morphological characters of the process begin to become apparent. Reverting to the appearances of the early stage of involution, as in Fig. 7, it will be seen that the process in the epithelium is one of vacuolation. The substance of the cell is transformed into a cavity filled with a fluid, and a certain portion of the cell's substance remains as the wall of this cavity and as a peripheral mass, which colours like the original nucleus. Now, among vacuolated epithelial cells, there will be observed considerable differences in the bulk of the peripheral mass and in the thickness of the wall of the vacuole. In some cases, the former is a large cellular element, as in some of the cells of Fig. 6; in others it is a thin crescent-shaped line, which is distinguishable from the rest of the vacuole outline only by its property of staining. Cells of this variety may be seen *in situ* in Fig. 7. We are here in the midst of a series of gradations. In the vacuolation process there is evidently a correlation between the amount of the cell-substance that is devoted to the vacuolar or fluid product, and the amount

that is devoted to the cellular product. One extreme of this series is where the vacuole reaches the maximum, leaving the peripheral or cellular mass at its lowest possible amount; and the other extreme is where the vacuolar product is at its minimum, and the cellular at its maximum. Both of those extremes have an existence in fact; with the latter we shall have nothing to do at present, but the former is simply the perfect transformation of the mammary epithelium into milk, which has been called a deliquescence. Now there is evidently not one law for the function at its height and another law for the function in its subsidence; there is a perfect continuity between the full secretory activity of the gland in the lactation period, and the diminished secretory activity which carries the gland through the involution process to the resting state. The functional stimulus, whatever it is, is simply lowered in the course of involution; it is not that the secretory force abruptly ends when lactation ends, and that the subsequent changes in the secreting parenchyma are of a merely retrograde or degenerative kind.

The perfect transformation of the mammary epithelium into milk is therefore, in its essence, a process of complete vacuolation. But the significance of that fact is missed unless the vacuolation process be reduced to its proper place among the great cellular processes of the organism. If the vacuolation process be examined in those cases where its morphological features are most declared, it will not perhaps seem fanciful to describe it as an example of endogenous cell-formation.

Less has been said of endogenous cell-formation in recent writings than in the earlier days of the cell doctrine. The two kinds of cell-formation—that by fission or division and that by the endogenous mode—are less rigidly contrasted than formerly; in botanical works, especially, there are other and intermediate ways of cell-renewal and cell-multiplication enumerated. But the endogenous mode retains its place in the text-books of animal histology; and if there were any doubt as to its occurrence in the healthy body, an examination of certain pathological processes would at once establish its distinctness and its contrast to the more usual mode of cell-formation by fission or division. In a former paper, on the histogenesis of secondary tumours in the liver, I laid great stress on the part that the endogenous mode of cell-forma-

tion played in producing the tumour cells out of liver-cells. In Chapter VIII. I shall describe the same process as occurring still more distinctly in lymphatic glands infected from tumours; it has been often described by other writers as occurring in the lymphatic glands in almost every infective disorder. A study of the various forms of cells undergoing the endogenous process in the liver led me, in my first paper, to compare them with the vacuolated cells of other pathological conditions, and with the vacuolated cells that are found in certain healthy processes which I enumerated. These resemblances seemed to me to point to a theory of secretion, and I concluded that the formation of secretion in epithelial cells was "essentially a process of endogenous cell-formation." It would require a large collection of facts, gathered especially from comparative physiology, to show some probability for this hypothesis as applied to all secreting cells, and I now limit my statements to the secretion of the breast.

When this view of secretion first occurred to me, I searched for some earlier statement to the same effect, and in an article by Professor Virchow, written in 1852, I found a quotation from another writer that appeared to be directly to the point, and which I referred to at the time as supporting the view I had independently taken up. According to Virchow, it was maintained by Friedrich Will that "all secretions proper are produced by means of cell-formation, and in fact by means of endogenous cell-formation (*durch Zellenbildung, und zwar durch endogene Zellenbildung vermittelt*)." The first part of the statement is nothing more than the generalisation that Goodsir first clearly laid down. But the second part of the statement, although it might be inferred from many of the facts that Goodsir collected, is at variance with his conclusion that "growth and secretion are identical," and must be regarded as a distinct addition to the cellular theory of secretion. In making the above quotation from Will, Virchow adds: "It is to be hoped that the proposition thus broadly stated is to be taken as applying only to the secretions of invertebrate animals; but it seems, at any rate, to indicate the wide distribution of a phenomenon that has perhaps an increasing significance in physiology, and which may lead us in course of time to regard the process of secretion from a higher and more general point of view[1]."

[1] Virchow's *Archiv*, III. 224.

That surmise can hardly be said to have proved correct. In so far as modern text-books of physiology touch upon the cellular side of secretion, they give a merely descriptive or pictorial account of it. The following example, quoted from a work mainly pathological, may be taken as showing how much progress has been made in the cellular theory of secretion[1]: "C'est ainsi que dans les glandes de l'estomac on voit des cellules primitivement cylindriques devenir sphériques en se gorgeant de sucs, tomber dans la lumière de la glande et se détruire en laissant échapper leur contenu." A more complete chapter of accidents, a more gratuitous tragedy, could hardly be pictured. But if precisely the same series of events be interpreted by the law of endogenous cell-formation, and if that mode of cellular activity be viewed in contrast with the other great variety, viz. by fission or division, we get an account of the process of secretion which may be called rational as compared with the one just quoted. What distinguishes the endogenous kind of cell-formation is the production along with the young cell of a vesicle or vacuole containing a fluid; in cell-formation by division the parent cell simply breaks up into two or more young cells. One may say that in the endogenous variety there is a provision for a fluid product along with the solid or cellular; and it is according to many analogies in nature of the adaptation of a general plan to particular ends that such provision should be magnified into the essential feature of the process. Whether it is in this sense or in some other that Will speaks of secretions as being produced by means of endogenous cell-formation, I have been unable to find out, not having had access to his original paper.

The foregoing paragraph is for the most part a repetition of what I wrote in the paper already quoted[2]. The more extended study of the secretion of the breast, in particular the study of it throughout its periods of subsidence and restoration, enables me to maintain this view of the mammary secretion with greater confidence. Not only is vacuolation seen to be the true morphological change in the secreting cell, but, as the function subsides, there is found an actual and even abundant production of cells from the epithelium, within or along with the fluid-containing vacuole; and

[1] *Manuel d'Histologie Pathologique* by Cornil and Ranvier, p. 35.

[2] *Report of the Medical Officer of the Privy Council* for 1874, p. 110.

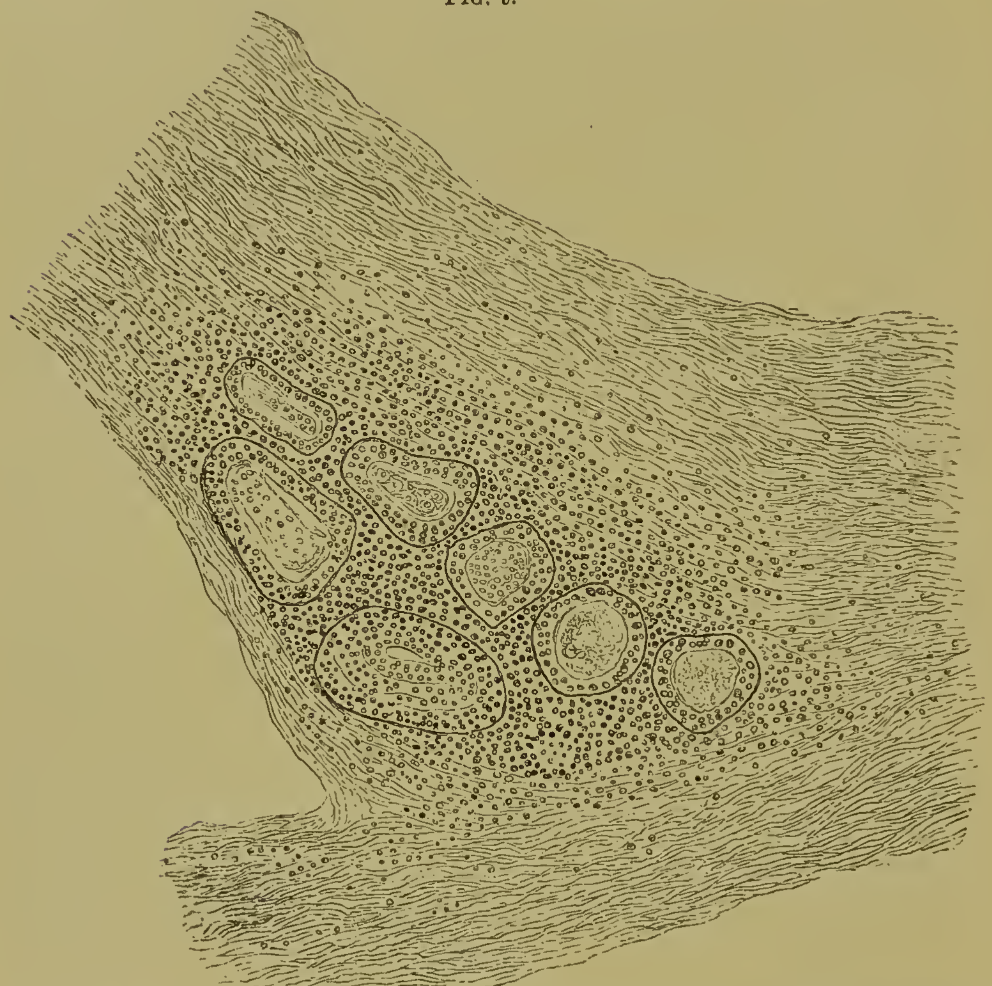
the weaker the function becomes, the greater is its cellular product. It is in the middle period of the subsidence that the endogenous kind of cell-activity is unambiguous. But from knowing the mode of action in the intermediate terms of what is evidently a continuous series, we are enabled to determine what is essentially the process in the extreme terms of the series. The expression that takes in all the phases of activity in the mamma, from the perfect secretion through the subsiding period to the resting state, is to call the process a process of endogenous cell-formation. What may be called the law of the secretion is the law of endogenous cell-formation.

Having finished the discussion of this more or less abstract but by no means unimportant point, it will now be convenient to introduce certain additional facts which have been omitted in the description of the involution process. These relate to the cellular products of the subsiding secretion of which mention has just been made. They will be frequently mentioned in the sequel under the name of waste products : in the physiological chapters the various normal circumstances under which they are produced and the manner of their safe disposal or utilisation in the organism will be fully described; in the pathological chapters their excessive production, or their production out of due season, or their retention at or near their place of origin will be found to be among the chief factors in the causation of tumours of the breast, and the mode of their production by endogenous cell-formation will be made to furnish a theory of their heteroplastic nature or of the malignancy of the growths which they help to build up.

Fig. 9 represents a section through the corner or angle of a mammary lobule. The preparation was made from a ewe that was killed three weeks after giving birth to a dead lamb and that had not been milked. At that period, three weeks after parturition, the udder was still of considerable size, and a clear brownish fluid could be expressed from the teats. The microscopic examination showed in many points a resemblance to the condition of which Fig. 5 is a drawing; there was a corresponding alteration of the epithelium, and many acini contained a fluid which coloured purple with the logwood and was on that account to be taken to be of a mucous nature. But the distinguishing

feature of the case was the enormous number of lymphoid cells which were met with both in the acini, in the spaces immediately outside them (known to be lymphatic spaces)[1], and in the interlobular fibrillar tissue.

Fig. 9.



From the udder of a ewe that gave birth to a dead lamb and was not milked. The condition three weeks after parturition: a group of seven acini forming the corner or angle of a lobule; many small round cells in the spaces round the acini and in the fibrillar tissue; mucus, mixed with small round cells, in the cavities of the acini. Magnified 150 diameters.

The section represented in Fig. 9 passes through the extreme pointed end of a lobule, and includes only seven acini; the interlobular fibrillar tissue is for the same reason cut obliquely, and appears thicker than it really is. The fibrillar tissue will be seen to be crowded at certain points with lymphoid cells, often ranged as if in a procession. The spaces round the acini, which in the active secretory state are reduced to a mere line, are here

[1] Coïne (Soc. de Biologie, 21 Nov. 1871).

seen to be broad tracts crowded with the same lymphoid cells; it is not unfrequently found in the preparations of this case that the contour of the acinus is completely obscured by the number of small round cells about it. The cells are for the most part round nuclear bodies, but there are found among them the various shapes given in Fig. 6. On closer examination, it is not difficult to find everywhere traces of the vacuolation or endogenous process within the acini, and it is hardly to be doubted that all of those small round cells are derived from the epithelium by that process. The case is one in which the cellular product of the vacuolation or endogenous process is the predominant, and it will be noticed that the accompanying fluid product is not the fatty fluid of the perfect secretion, but a mucous or albuminoid fluid[1]. The case shows a production of cellular elements from the epithelium which is excessive for that stage of involution, and the fact of the animal never having been milked is perhaps the modifying circumstance; but the same phenomenon is found to occur in other cases in corresponding stages of the involution process. It will be observed that the greater number of the cells have escaped from the acini into the extra-acinous spaces and the fibrillar tissue, and it is only in those situations that they can be observed in any quantity; but it is probable that the ordinary outlet of the ducts, which are still patent in that stage of involution, must give exit to many of them along with the fluid that is produced at the same time, and which was found in the ducts. Reverting to the case from which Fig. 5 is taken, the same appearance is seen to a more limited extent. There are here and there in the tissue outside the acini considerable heaps of lymphoid cells; and among them are found other and thoroughly well-marked waste products of the involution process, which enable us to place the subject on which we are now entering on a perfectly sound basis of evidence.

The account given provisionally of the completion of the involution process was that the acini, denuded of their perfect mosaic of epithelium, gradually closed upon the nuclear elements that survived from the vacuolation of the latter, and so conducted the gland to the resting state as figured in Fig. 4. If

[1] "After the secretion of milk has ceased, the secretory structure is often loaded with mucus."—Astley Cooper, *Anatomy of the Breast.*

that were the entire process, we should still have to account for the escape or discharge of a certain quantity of cells from the acini; for the resting cells of an acinus are much fewer in number than those that cover its floor in the middle stage of involution. For example, in the case from which Fig. 5 is taken, there are found considerable tracts of acini which have already contracted their circumference to some extent, and there is to be seen at one or two places a lobule which has for some reason or other advanced beyond the others, and reached the extreme contracted state of involution. In such a lobule the cells within the acini are extremely few, from four to six in the section. But what arrests the attention at once in looking at this lobule is the presence in it of a quantity of bright yellow pigment. On closer inspection the pigment is seen to be for the most part scattered about the cells inside the acini; and if we leave this involuted lobule and search in less advanced parts of the gland, the source of the pigment and the significance of it become clear enough. The other class of waste products which were referred to above as being thoroughly well marked and as affording a sound basis of evidence for the entire question of epithelial waste products, are large granular nucleated cells filled with a bright yellow or golden pigment. The nucleus is often visible; and when it is stained purple with logwood, the cell with its purple nucleus and its bright yellow substance becomes to the microscopist a striking and pleasing object. Fig. 10 represents a very common appearance of the large yellow cells. The lobule is in a somewhat contracted state; in several of the acini the pigmented cells, which are represented in the woodcut simply as granular, may be seen *in situ;* while a considerable number of them are seen to occupy the interfibrillar spaces outside the acini and the lobule. The latter situation is most characteristic of them. The figure is not taken from a gland known to be in the process of involution; on the other hand it probably represents an early stage of evolution. But it is inserted here to show once for all the large yellow granular cells to the best advantage as regards their size, shape and general appearance, so far as a woodcut can reproduce them.

Out of a great many preparations of the involution process it would be difficult to find one in which the origin and destiny

Fig. 10.

Lobule of a mamma near the resting state. Numerous large pigmented cells within the acini and in the interlobular fibrillar tissue; sections of three blood-vessels to the left of the lobule. Magnified 160 diameters.

of the pigmented cells together with their place in the involution process were at once apparent. They are not unfrequently seen in the tissue outside a lobule in rows three or four deep; again they are found in the interfascicular spaces among the lymphoid cells that have been already mentioned. Inside an acinus they are found seldom in greater numbers than one or two, but in that position they do not always possess the definite characters that they often show elsewhere. What one sees inside an acinus is, as it were, certain round discs or other irregular forms of pigmented substance generally bestowed round a nucleus; this is a common appearance in the preparation from which Fig. 5 is taken. Finally, as has been already said, the same preparations show, in the involuted lobules that they contain, a more or less amorphous appearance of the pigment within the acini, and in sets of preparations from other animals (especially the rabbit), showing the advanced involuted state, the surface of the involuted lobules is found to be strewn with numerous grains of pigment of a brownish colour. Putting together these facts collected from the involution process alone, a theory of the origin of the pigmented cells might be made out. But the question of their origin and significance is greatly simplified by anticipating so far the study of the evolution process and of certain pathological

processes. A drawing of one of the latter may here be inserted. Fig. 11 is the section of a pathological lobulus from the bitch:

Fig. 11.

A pathological lobule. The uppermost acinus shows the pigmented cells as epithelium *in situ*. Magnified 160 diameters.

the circumstances of its occurrence do not require to be stated here. It is found among lobuli most of which show the ordinary appearance of the resting mamma; and this particular lobulus, though three or four times the size of its neighbours, has retained its proportions exactly. All the acini of this lobule have a yellowish tint; but the attention is chiefly directed to the half acinus that is uppermost in the figure. In it the cells are yellow and granular, and most of them show a nucleus; they are also for the most part columnar or club-shaped. They occupy the position of the normal mammary epithelium, and the pathological form that they have acquired makes them, if one may so speak,

more epithelial than the mammary epithelium usually is. Yet they look as if they were about to be shed from their epithelial situation, and as a matter of fact the same cells, with trifling modifications of form, are to be seen in considerable numbers in the adjoining fibrillar tissue. In the pathological part of the work many other instances will be given of this peculiar transformation of the epithelium; what is here desired is simply to show the epithelial origin of the pigment-cells of the mamma. So conclusive are all the appearances bearing on this question, that it may be stated in the broadest manner that, whenever those large yellow granular cells are found in the mamma, they are of epithelial origin.

Having so far stated the evidence for the uniform occurrence of the large granular pigmented cells in the course of the periodical involution, and having described their more general characters, we come now to consider what is the exact place that is to be assigned to them in the involution process, and by what considerations they may be brought within the operation of the general law of the secretion, that is to say, the law of endogenous cell-formation.

As the large colostrum-like cells that are figured in Fig. 8 characterise an early stage of involution, and as the more distinctly nuclear products of vacuolation of Figs. 6 and 9, together with the accompanying mucous fluid, characterise the subsequent stages, so the pigmented cells are found to be characteristic of the last state of involution, and the pigment that belongs to them is to be found strewn over the lobules that have reached the resting state. It has up to this point seemed a satisfactory account of the involution process to say that the acini contracted their space and retained within them a certain number of the cellular bodies that remained over from the vacuolation of the epithelium. But the unexpected introduction of a set of pigment-bearing cells is precisely one of those matters of observation wherein the actual course of nature proves more varied than had been conceived, and whereby we are led to enlarge very considerably our view of the process.

In reviewing the process of involution in the mamma, it might appear at first sight as if the entire cycle of changes in the epithelium, that conduct the gland to the resting state,

took place in one and the same set of cells. When lactation stops, the acini may be imagined to possess a mosaic of perfect epithelial cells which have not followed their predecessors in transforming their substance into milk, but which are destined to be the elements that the resting cells of the gland are, after a prolonged process, formed out of. But a cursory view of the facts will at once show that such is not the case. A preparation has been already described, belonging to an early stage of involution, in which many of the acini had a complete set of vacuolated cells lining their wall, and another collection of similar cells lying free in their lumen; and this fact can mean nothing else than that the cells now in the cavity of the acinus had been shed from their epithelial situation, and had been replaced by another set. In like manner the various forms of cells that characterise the various stages of involution must have resulted from a transformation *de novo* of the renewed epithelium, and not from successive changes upon the same cell. Thus, it is difficult to imagine the peculiar pigment-transformation of the epithelium to be anything else than the direct and sole change that those particular cells undergo. They are evidently products *sui generis;* they are the kind of cells proper to the later stages of involution; and it may be asserted, by way of illustration, that if the functional stimulus of the gland always remained at the same low intensity that it has in that stage of subsidence, the gland would produce nothing but those cells. The notion then must be set aside, that the particular set of cells that the gland possesses when lactation stops, are the same which become, after various transformations, the resting cells at the end of involution. The epithelium, which had been constantly renewed during lactation, is renewed also many times before the involution is completed, and before the functional activity subsides. In other words, the formative or plastic activity of the gland goes on so long as its functional activity goes on. As the latter gets weaker, the former gets slower, till a point is reached when there is no further renewal of cells within the acinus, and those last produced remain almost without change.

Thus, in concluding the descriptive account of the process of involution in the mamma, we are left with the important physiological fact that the periodical subsidence of the function

is accompanied by a considerable production of cellular waste material. In the earlier stages of involution it is thrown off in the form of the cells that are drawn in Fig. 8, and that class of waste products doubtless find their way out of the gland by the ducts. The cells in Fig. 9, along with the variously shaped peripheral masses of the vacuoles, may be taken to represent the waste products of a later stage, and it is seen that the lymphatic circulation is at least one mode of their disposal. Lastly, towards the end of the process there are produced the very remarkable yellow cells, and these also find their way out of the gland by the lymphatic channels. The complete description of the removal of the cellular waste of the secretion by means of the lymphatic circulation is postponed till the evolution process has been described.

There remain for discussion, in connexion with the process of involution, two points of a theoretical nature. One of these will deal with the considerations by means of which the phenomenon of the large granular pigmented cells can be brought within the law of the secretion, which is held to be the law of endogenous cell-formation; the other point may be briefly disposed of at once.

In the state of active secretion of the mamma, it is convenient to suppose that each epithelial cell that is used up in the formation of the milk has been at one time a perfect polyhedric cell of a homogeneous or finely granular protoplasm and with a central nucleus, and that it has rapidly undergone the cycle of changes whereby its whole substance has been converted into milk. But it is not necessary to suppose that the same should be the case when the function is not at its full force, and is in fact slowly subsiding. The plastic or formative activity of the epithelium must continue, as has been argued, so long as the functional activity has not entirely come to a standstill. But it is not at all probable that the same perfect mosaic of polyhedric epithelium is reproduced at every successive step throughout the whole period of involution as well. For example, if the plastic activity of the gland be viewed for a moment, apart from the functional, and if a point of time be taken, say towards the end of involution, it is not to be supposed that the acini of the gland, at that point of time, would be clothed with a

layer of perfect polyhedric epithelium. On the contrary, the nearer is the approach to complete cessation of the gland's activity, the more crude, so to speak, are the successive renewals of the epithelium. The importance of this theoretical statement will appear when the process of evolution is described.

The other theoretical point reserved for consideration relates to the pigmented waste-cells.

As we were led to view the ordinary transformation of the epithelium into milk as a process of extreme vacuolation and to refer it to a place under the law of endogenous cell-formation, so we come, at the other end of the scale, to refer the phenomenon of the granular pigmented cells to the same law. The superficial objection to calling the production of milk a process of endogenous cell-formation is that there is in it no actual formation of cells. The objection to classing the granular pigmented cells among the same phenomena is that there is in them nothing endogenous or vacuolar. The explanation of those apparent anomalies is furnished by a method of proof that has already been put in force. Directing attention again to the well-defined vacuolation process in the cells, which marks the middle stages of involution, it will be seen that various degrees of vacuolation of a cell occur, and that there is a correlation between the extent of the vacuole and the extent of the associated cellular mass which is generally on the periphery. It often happens that the vacuole is large, occupying almost the whole substance of the cell, and that the solid part of the cell, that part of its substance which gives it an individual existence and a shape, is nothing more than a delicate ring (in profile), with a slight crescentic thickening of coloured substance at one side. It is by observing the varieties of this peripheral coloured element of the vacuolation that the significance of the process becomes clear. Instead of being a thin rib-shaped or crescentic body, it is often of a rhombic or of a hemispherical form, while the latter forms shade off gradually into the round nuclear bodies which are sometimes found lying as if on the ring of the vacuole, but often also found as free cells in its centre. Again, cells are now and then found that have both the crescent-shaped peripheral mass and the free round cell in the vacuole, and this may be considered as the most comprehensive type of vacuolation. Here, then, the process is evidently the process of cell-formation by the endogenous mode; and

if the vacuoles of secreting cells were only found to contain several small round cells in their cavity, instead of one, the most rigid and inelastic conception of endogenous cell-formation would be completely satisfied. But the plurality of free round cells in the vacuole, although it is often held to be an essential part of the definition of endogenous cell-formation, seems to be oftener a pathological phenomenon than a physiological. Regarding, then, the epithelial cell which is subjected to this process as containing a fixed quantity of substance, the more of it that is devoted to fluid transformation, the less is the amount of the co-ordinate cellular product, and *vice versa*. There is a vanishing point for each of the two factors in the process respectively. The one vanishing point is where everything is fluid, the other vanishing point is where everything is solid; and yet the law of the cell's activity is the same in those extremes as in the intermediate degrees. Both of the vanishing points have an existence in fact. The perfect formation of milk is the one, and the purely solid product of the epithelium is the other; the one coincides with the full force of the functional excitation, the other with its extreme enfeeblement[1].

There are several matters of observation in connexion with the granular pigmented cells that require to be stated, in order to redeem the somewhat theoretical, and, it may still appear, fanciful account of the conclusion of the involution process. In the mamma of a cat that was killed four weeks after the young were taken away, the acini were found considerably reduced in size; they con-

[1] Goodsir, in his Memoir on Secreting Structures (*Anatomical Memoirs*, Vol. II. p. 422), drew many of his conclusions from glands in the lower animals, such as the testicle, that have periodical seasons of activity. One of his conclusions is as follows. "There are three orders of secretions: (1) A true secretion —that is, matter formed in the primary secreting cell-cavities; or (2) A mixture of fluid formed in these cell-cavities with the developed or undeveloped nuclei of the cells themselves; and (3) it may be a number of secondary cells passing out entire." A liver follicle in a crustacean showed the three orders of secretion at one and the same time. "The blind extremity of the follicle is slightly pointed, and contains in its interior a mass of perfectly transparent nucleated cells. From the blind extremity downwards these cells appear in progressive states of development. At first they are mere primitive nucleated cells; further on they contain young cells; and beyond this they assume the characters of primary secreting cells, being distended with yellow bile, in which float oil-globules, the oil in some instances occupying the whole cell."

tained, very uniformly, ring-shaped vacuolated cells, but they had everywhere as well a yellowish colour, and the yellow tint did not extend to the other tissues of the gland. On closer examination it seemed that the yellow colour was in the fluid contents of the vacuoles, and there appeared to be traces of the yellow granular cells in the fibrillar tissue outside the acini, in the same position as they are clearly seen to have in other preparations better adapted for the purpose. Unfortunately the appearances in this case were always somewhat indefinite, although several sets of preparations were made from it. But to supplement that defective evidence, it may be stated, that in a remarkable case, to be mentioned hereafter, there was found distinct vacuolation of the pigmented cells outside the acini, the fluid contents of the vacuole being distinctly yellow. Again, in the case of a cat nine days after the end of lactation, which has been used for illustration several times already, the yellow granular substance within the acini seemed to break up into a number of round disc-like bodies. It is not desired to follow this subject at present further than to recall the fact that the pigment of the granular cells is not unfrequently seen strewn over the involuted lobules, having the appearance of amorphous grains of hæmoglobin. The resting cells of the acini, or at least some of them, are in all probability the surviving nuclei of the granular pigmented cells; the latter have given up their pigmented cell-substance, but their nuclei remain. These facts point to a lingering secretory activity in the epithelium that is transformed into pigmented cells. But the greater part of the large yellow cells are thrown off from the acini entire, and find their way out of the gland entire. Their functional importance is, as it were, so slight, that they are actually thrown off from the gland before any function is performed; and this consideration leads me to speak, in the briefest possible manner, and as a conclusion to the first part of the inquiry, of the significance of the solid or cellular products of the epithelium as regards the function.

From the functional point of view, or from the standpoint of usefulness, the fluid product of the epithelium is the only one of the two that is properly speaking a secretory product. But the other or cellular product is all the while potentially present; and it is precisely when the fluid product ceases to be useful or to be required, that the cellular product asserts itself. This cellular

product, so far as the facts up to this point carry us, does not become itself useful in its turn; it is indeed spoken of as a waste product. But the formation of the useful product cannot come to an end without the temporary formation of a quantity of waste material. The periodical subsidence of its function costs the mamma a good deal of useless cell-formation, and we shall have occasion to show immediately that the re-establishment of its function, extending over a longer period, costs it a good deal more; while the waste cells produced in both of those processes (and in all other enfeebled conditions of the secretion) have it in their power to become, and sometimes do become, highly dangerous elements of disease.

CHAPTER II.

THE PERIODICAL EVOLUTION OF THE BREAST.

It has been already explained that the term "evolution" of the mamma is used to describe the periodical process by which the gland, after each period of functional rest, is step by step rehabilitated with its full structure, in readiness for the next period of suckling. In an animal killed a day or two before parturition the mamma is found to possess fully expanded lobules and acini, and the acini to have the mosaic of perfect epithelium. Preparations of the mamma at this period are in fact better fitted to show the perfect form of the epithelium than preparations taken from a gland in the full course of lactation. The beginning of the evolution process must be held to coincide more or less exactly with the beginning of pregnancy. Important changes in the gland are observed at early periods of pregnancy, and the evolution is found to proceed, in its later stages, so exactly hand in hand with the growth of the embryo, that it is convenient to suppose the first step towards the preparation of the gland to be contemporaneous with the early changes in the uterus, although, as a matter of observation, little or no alteration of the resting state is found till the embryo is somewhat grown. We thus arrive at the important fact, that the evolution process is an exceedingly slow process, in respect of the object to be attained, and that it occupies, generally speaking, the entire period of gestation.

The evolution process, as about to be described, has been studied chiefly in the cat. Casual preparations have also been made from the sheep and guinea-pig, and a large amount of confirmatory

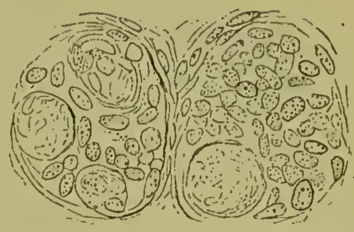
evidence has been obtained from a series of cases in the dog, which were made use of under the following circumstances. A number of cases of mammary tumours in the bitch were collected for the purpose of pathological study; the tumours for the most part affected only a limited area of the chain of glands on one side. In several of the cases the entire chain of glands was obtained, the animals having been killed in anticipation of a fatal termination of the disease. It was found, on carefully examining the other cases of tumours, which were removed by operation, that nearly all of them had distinct fringes of mammary tissue around them, which, by the side of the tumour, was to be accounted normal. Those cases, fifteen in all, certainly did not, so far as was known of the history of the animals, exemplify the physiological processes of evolution or of involution. But the microscopic examination showed that they were each of them the subject of a certain feeble kind of activity, which often resembled that of the earlier stages of the evolution process, although the excitation to it was not the same. They seemed to show, in fact, that whatever was the stimulus that stirred up the dormant activity of the gland, it commenced in the track of the evolution process, and that it rarely got beyond the earlier stages of that process, but continued to act upon the gland, so long as it lasted, at a uniform low degree of force. As regards the origin of the tumours, sometimes multiple, that occurred in portions of the chain of glands, this feeble activity was of the highest significance, while the cases were at the same time found to illustrate those effects of weak functional stimulus that are found in the physiological processes, and to coincide rather with the commencing stimulus of the evolution process than with the subsiding stimulus of involution. The series of cases in the cat on which the account of normal evolution is mainly based were eleven in number; two of these were known to be cases of *primiparæ*. They were fairly representative of various stages of pregnancy, as estimated by the size of embryo. The newborn kitten may be taken to be about 5 inches long, measured to the root of the tail. The youngest litter were 1½ inches long, and the intermediate sizes of 2½, 3, 3½, and 4 inches, were found, as well as fœtuses almost full grown. There was on the whole a remarkable correspondence throughout the various cases between the size of the fœtus and the stage of evolution of the

mamma in the parent. Thus in two sets of fœtuses that were nearly 5 inches long and with the hair grown, the mammæ of the parents showed the most minute resemblance, and they both resembled the condition in the udder of a ewe that was pregnant with a fœtus about 10 to 12 inches long. Again, the mammæ corresponding to the fœtuses 3 to 4 inches long had all an equally characteristic appearance. Greatest diversity occurred in the earlier stages of pregnancy. Thus, in a cat with fœtuses 2½ inches long the mammæ were found in a condition not further removed from the resting state than in a cat with fœtuses of 1½ inches, and considerably less advanced in evolution than in a third cat that had also 2½ inch fœtuses.

The three cases last mentioned, taken together, represent the earliest appreciable progress towards unfolding, and the condition found in them will now be described. In naked-eye characters the glands differed little from those in the resting state. Their substance was of no great thickness, tough on section, and with the gland-tissue proper separated into islands or bands by tracts of connective tissue, with or without fat; the larger ducts could be seen radiating towards the nipples, and the open mouths of them and of large vessels were conspicuous in cross sections. On microscopic examination the acini had already advanced from the resting state both in size and in other particulars. In point of size they were perhaps half that of the perfect acinus; the infundibular or trefoil-like appearance of three or more acini communicating was much more frequently observed in these preparations than in those of any other condition of the gland, and this circumstance made it difficult sometimes to estimate the size of a single acinus. The cells within the acinus were many of them the same as the round or oval nuclear bodies of the resting state, although more numerous; they occupied the cavity of the acinus generally. But among the nuclear cells were a few of a totally different kind. These are no other than the large yellow granular cells that have been already described as characterising the later stages of involution. Fig. 12 is a drawing of two adjacent acini from the mamma of a cat with fœtuses 2½ inches long; it will be seen that one acinus contains three of the large pigmented cells and the other a single large cell. It is to be added, in explanation of the figure, that the large cells have exactly the same yellow colour as the

corresponding cells of involution, and that some of them appear to have two or even more nuclei at different parts of their periphery. It is necessary, before proceeding further with the account of these earliest products of evolution, to repel an objection that may be made. There is no danger of mistaking them for the last products of involution, the existence of which has been already proved. It is true indeed that traces of pigment remain in the gland after the involution process has been completed; but it is either in the form of the entire pigmented cells which are still detained outside the lobule in their passage from the gland, or it is in the form of grains of free pigment scattered over the surface of a lobule, or lying among the resting cells of an acinus. Except under those circumstances the yellow pigment is not present in the gland after involution is completed, and there can be no doubt that the large yellow cells found within the acini in the early stage of evolution are characteristic products of that stage.

FIG. 12.



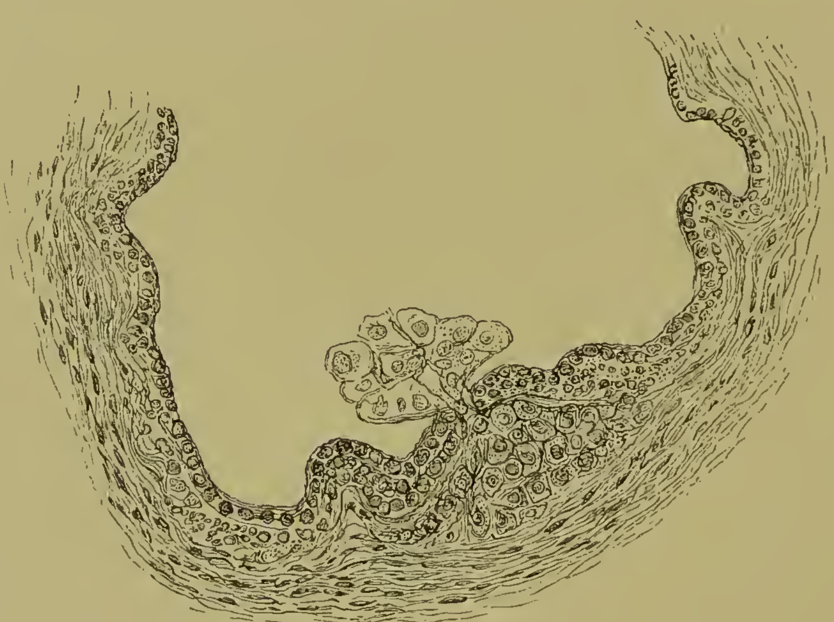
A pair of acini from the mamma of a cat pregnant with fœtuses 2½ inches long. The acinus on the left hand contains three large yellow cells, and that on the right contains one. Magnified 300 diameters.

In the three cases with small fœtuses, grouped together as representing the first stage of evolution, the pigmented cells were found in large numbers, indicating a very considerable cellular productiveness of the acini, and there were certain instructive differences as to the situations in which they were found. In the most advanced of the three, the lobules were considerably expanded, and the acini showed a distinct central space and a regular arrangement of the cells round the wall; there was in fact an appreciable advance in evolution, and the condition came very near that which will be described as characterising the next definite stage of the process. Now, when the teats of this animal were squeezed, during life, to find out whether the gland contained milk, there issued from the teats not a fluid substance, but a solid friable substance of a yellowish-brown colour in the shape of cylinders or plugs, which broke off in short pieces as they reached the orifice of the nipple[1]. On examining this substance with the microscope, it was found to consist of rounded masses or oblong casts, in neither of which was the form of individual

[1] I am told that the same thing is of regular occurrence in cows that are in calf.

cells easily made out. On proceeding with the dissection and exposing the mammæ *in situ* the ducts were seen radiating from the periphery towards the nipples, as they are often seen where the gland has not its full expansion; but in the present instance they were obviously filled with a yellow material, the same as was expressed from the nipple. The yellow contents were readily seen in the stained sections of the prepared gland, and they were found to consist of closely-packed masses of the large yellow cells. In the same preparations the yellowish cells were seen to be still within the acini at certain points; they were also found, as they very commonly are, in the interlobular fibrillar tissue. But the

Fig. 13.

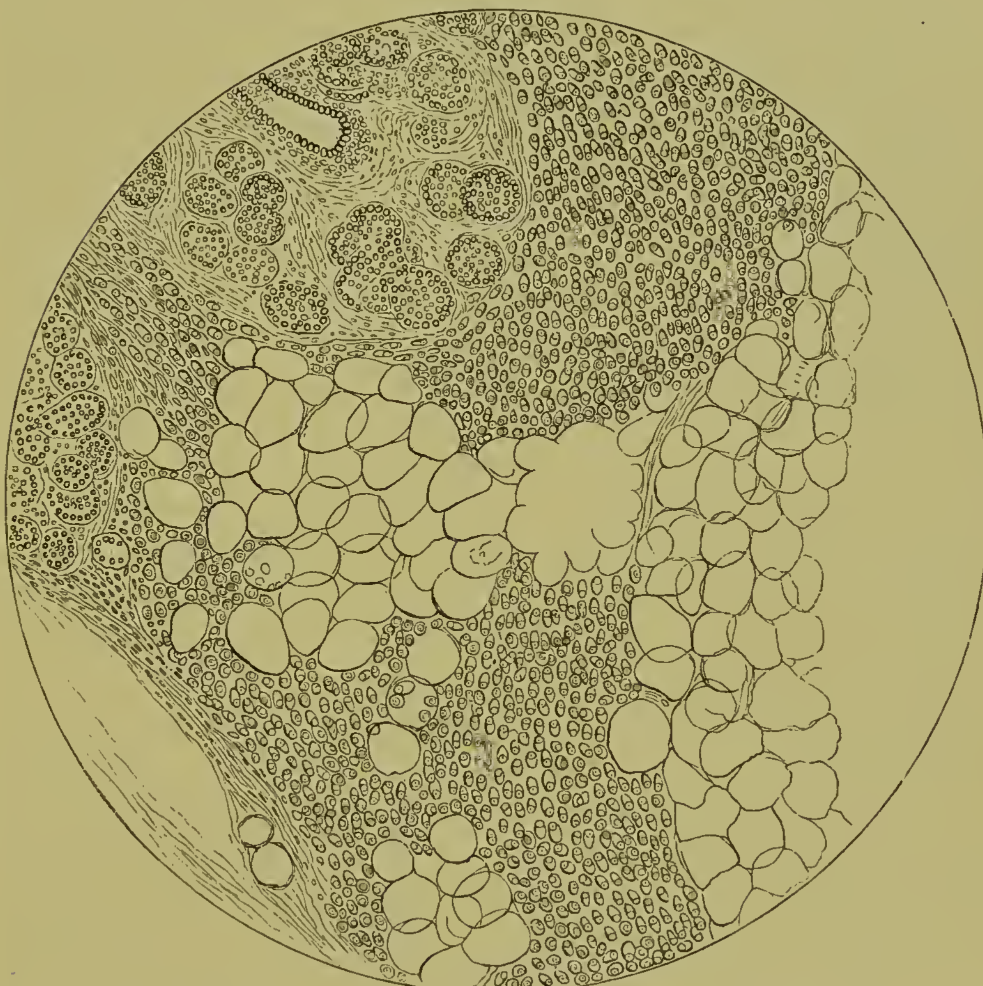


From the mamma of a cat pregnant with fœtuses 2¼ inches long. Oblique section of a duct, showing collection of large yellow cells in its submucosa, and the same bursting into its lumen. Magnified 150 diameters.

most remarkable position in which they were found was the loose submucous tissue of large ducts. There they occurred closely packed together in one or more rows, and in two or three places where they were collected in the submucosa in largest numbers, was observed the singular appearance of which Fig. 13 is a drawing. A rounded cluster or knob of the characteristic yellow cells, for the most part with a nucleus visible, is seen to have burst through the epithelium into the lumen of the duct, and to be

followed up by several rows of the same cells in the submucosa, converging towards the breach in the epithelial wall of the duct through which the others had already passed. There is no doubt that a very large number of the pigmented cells in this case left the gland by way of the ducts, and that they entered the latter, not directly from the acini, which were probably not in open communication with the ducts at the time when the yellow cells were

FIG. 14.



From the mamma of a cat in an early stage of evolution. The left-hand side of figure shows portions of two lobules, and the rest of the figure shows the fat tissue outside the secreting structure crowded with *the large yellow cells.* Magnified 90 diameters.

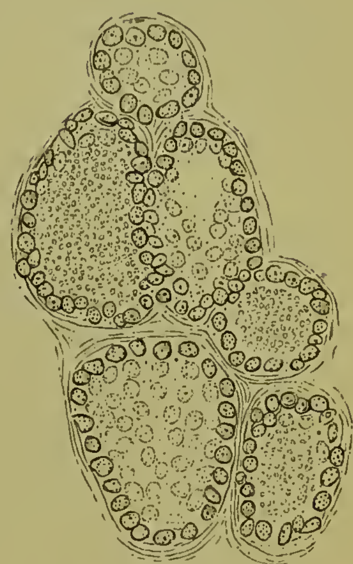
being formed, but by first escaping through the wall of the acinus, then traversing the submucous tissue of the duct, and finally breaking through into the latter at a convenient place. But that is certainly not the only mode of their escape from the gland;

it has been observed in the preparations of this one case only, and it probably belongs to a later period of the evolution when the perfectly free communication between the acini and the ducts is being re-established. Fig. 14 is from another case in the cat, with fœtuses 2½ inches long, and though it will have to be referred to again, it is introduced here to show the very considerable numbers in which the large pigmented cells are thrown off in evolution, and the mode of their disposal. The left-hand side of the figure shows portions of two lobules; with a higher power it may be seen that some of the acini contain the large yellow cells in their interior, and, indeed, the two acini of Fig. 12, which contain several yellow cells, are drawn from another part of the same preparation. Between the two lobules the fibrillar tissue is occupied with a procession of those pigmented cells, along with a number of round and elongated nuclear cells, which have no pigment around them. The right of the figure shows an enormous collection of large nucleated cells, which are all of the same pigmented kind. They have penetrated into the fat tissue about the gland in the manner that the figure shows. The cells have their nuclei almost uniformly at one end or on one side; several of the largest of them have two nuclei, also excentric, and a few of them are distinctly vacuolated, the vacuole containing a homogeneous fluid substance of the prevailing yellow colour. The case will not be further described until the general question of the disposal of cellular waste by the lymphatic channels is considered in the next chapter.

Proceeding to the next well-marked stage of evolution, a certain definite appearance of the gland is found to be common to the cases where the fœtuses were 3 to 4 inches long, and an approximation to it is found in some parts of the gland in the most advanced of the group of three cases representing the first stage. Fig. 15 represents this characteristic appearance. The acini are about two-thirds of their full size, and their arrangement in clusters within the lobule can be seen more clearly than in any other condition of the gland. The cells within them are still of the nuclear kind, that is to say, they have no broad fringe of protoplasm round them; and although there appears to be a definite short interval between each cell, those intervals cannot be said to be occupied by the cell-substance. They are, however, distinctly larger and more granular than the cells of the resting state,

and than many of the same class of nuclear cells in the stage that has just been described. They form a complete covering to the floor of the acinus, being arranged, as has been said, in regular order with definite intervals between them. It can readily be conceived that this orderly arrangement depends on the re-establishment of the regular meshes of the basement membrane, although the latter are not easily made out. A very regular polygonal meshwork of transparent fibres of uniform thickness has been seen in the very small acini of one of the cases in the tumour series, where the gland was in a condition resembling that of an early stage of evolution. Besides the regular order of the cells in the floor of the acinus, those forming the circuit round it, as seen in the profile view, are also placed in a regular line with short spaces between them. Another distinguishing feature of this stage is the presence in the cavities of the acini of a peculiar granular material, the coagulated condition of a fluid. In many acini it takes on the colour of the staining agent to a certain extent, in others it retains the character of highly-refracting granules, while in others it is found to be mixed with or to pass gradually into a fluid substance which is often vesiculated.

Fig. 15.



From the mamma of a cat pregnant with fœtuses 3½ inches long. Some of the acini contain a granular material. Magnified 300 diameters.

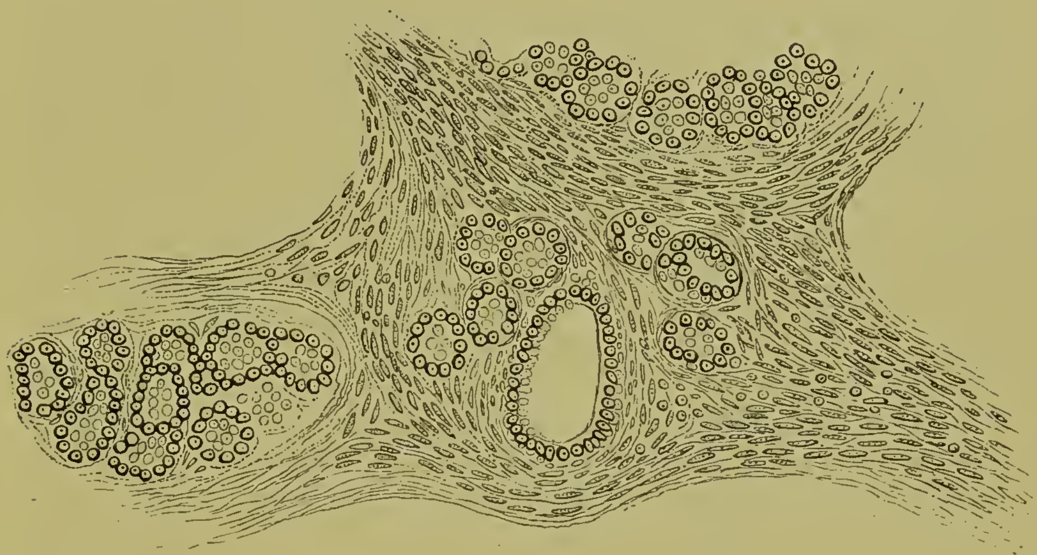
In the glands now under consideration, corresponding to 3 to 4 inches length of fœtus, the evolution has advanced to a point when there is no further trace of the large pigmented cells, whether in the acini or in the interlobular fibrillar tissue. In the former group of three cases, showing the early evolution changes, there was one that came nearest to the later stage of evolution, now being described; and in that case the pigmented cells were already collected in large numbers in the ducts, and were seldom met with at or near the place of their origin. The season of their production from the acini had already passed. But in the two other cases of the same group, which were known from other circum-

stances to be at an earlier stage, the pigmented cells within the acini were comparatively numerous. But although the later stage of evolution is not characterised by the presence of large pigmented cells in the tissues of the gland, it is characterised by the presence of no less important cells of another kind that are also to be seen collected in heaps or in transit along the interfascicular spaces. The absence of pigment in these cells makes it a more difficult task to prove their identity: that is, to prove where they come from and where they go to. There is, however, no room for doubting the existence of a general class of waste-cells of the secretion; the woodcut on page 43 shows an unmistakeable collection of them. If all the cells that fell to be described under the category of waste-cells were of the pigmented kind, the doctrine of a cellular bye-product of secretion might be established by a simple demonstration. So far as the pigmented cells go, they are evidence of a crude or cellular secretion produced at a time when the function has all but come to rest, and again when it has just begun to revive. That there should be corresponding crude products of the secretion at other stages of the subsiding or reviving function is in itself highly probable. The difficulty of actually proving their existence lies in the circumstance that they have no distinctive mark such as the pigment of the more immature cells, and that they are in size and form much the same as connective-tissue cells, fixed or amœboid, or as emigrated colourless corpuscles of the blood. The last-named need not be seriously considered; they are not all white corpuscles that have the appearance of white corpuscles. But the connective-tissue cells are a real source of ambiguity, and that ambiguity is well illustrated in the subjoined woodcut (Fig. 16). It cannot be said that the appearance therein drawn is of so convincing a kind as many other parts of the glands might have furnished. But it represents, at least, a common appearance in the interlobular tissue of breasts at the particular stage of evolution which, in the cat, corresponds to fœtuses about three inches long.

The figure shows the interlobular tissue, and to a certain extent also the interacinous tissue, to be crowded with oblong or spindle-shaped cells of granular substance and of considerable bulk or plumpness. They appear to lie loosely in the interfibrillar spaces. If they are to be compared to the connective-tissue cells of a healthy part, the comparison can only be with embryonic

connective-tissue cells; and in the mamma of a very young animal, even perhaps of a primipara, there would be a strong presumption that the cells belonged to the connective-tissue stroma. The animals in question are all marked in my notes as being full-grown, and I have no further information about them.

Fig. 16.



From the mamma of a cat pregnant with fœtuses 3 inches long. At the upper border is represented the outermost row of acini of a lobule; on the left, below, a small lobule; at the two sides, curves corresponding to the boundaries of two other lobules; in the centre, a duct with a group of acini round it; *the interlobular tissue crowded with oblong cells.* Magnified 160 diameters.

There is, however, a considerable body of evidence to support the view that the oblong and other cells in the interfibrillar spaces belong to the same class of waste-cells of the secretion as the unmistakeable pigmented cells already described. The strongest evidence is perhaps the fact that they are very commonly found mixed with the pigmented cells, and that the latter often assume the same oblong or fusiform shape. The left-hand side of Fig. 14 contains both kinds of cells crowded together.

Again, they are found in heaps at various points in the interlobular tissue, and in such accumulations it is hardly possible to mistake them for the fixed elements of the stroma. The heaps are circumscribed in extent, and the cells composing them are arranged in rows corresponding to spaces between the fibres of the stroma. The forms of the cells, also, are much less am-

biguous than those drawn in Fig. 16; they are rounder and sometimes cubical, and may be compared to the class of "parenchyma-cells" which have been described as part of the intertubular or inter-acinous structure of other glandular organs[1].

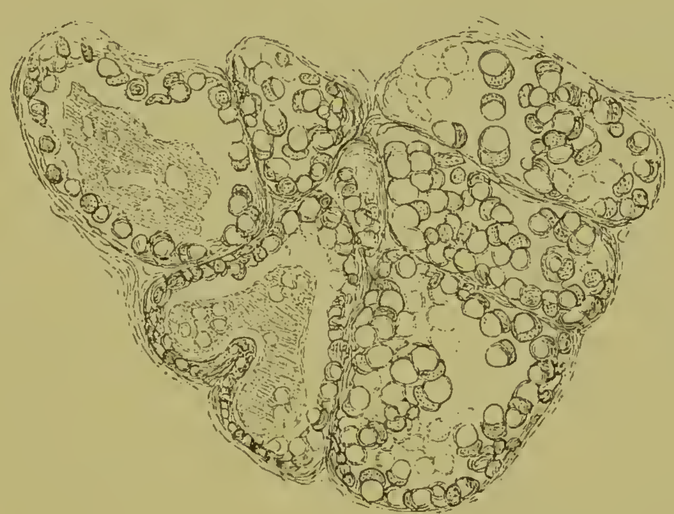
Another point in the evidence is that when the breast is examined at a later period of evolution, not indeed in the same animal but in animals of the same size and otherwise resembling, the stroma is found to be comparatively free of all such cells. But all of those more or less dubious proofs are superseded by the striking evidence derived from pathology. In the pathological processes, to be afterwards described, which have their physiological type in the normal process now spoken of, there is the clearest proof of the epithelial origin of cells in the stroma other than the pigmented cells. Not only oblong or fusiform cells, but large spherical and even cubical cells are found in rows and heaps outside the acini of the gland, and having a perfect likeness in all points to as many varieties of cells within the acini. To invoke the evidence of pathology at this stage is by no means to argue in a circle; there are good reasons why the morbid physiological processes should in some points more clearly reveal the law of the function than the healthy processes. The pathology is not borrowed from the physiology, but it hangs together with it. In like manner the phenomena of the subsiding process accord with those of the reviving process; and the facts relating to the disposal of the cellular waste of the secretion by means of the lymphatic glands complete the concurrence of testimony. Certain parts of the doctrine of waste cells of the secretion may be histologically weak, but they are

[1] I have lately met with the two following references to cells in the stroma, probably of the same nature as those described in the text; the authors, however, do not appear to have assigned any clear physiological significance to them, but have described them, after the "objective" fashion, as noteworthy points in the histology of the breast, and without reference to its periodical processes. Winkler (*Jahresbericht d. Gesel. f. Naturwis.* Dresden, 1874), describes "leucocytes" in the walls of the alveoli, and suggests that they play a part in the formation of the milk. Von Brunn (*Göttinger Nachrichten*, No. 19, 1874) found in the interstitial connective tissue of the breast in man and in the rabbit, and in that of the submaxillary gland in the ox, cells and groups of cells of the same character as those described by Hofmeister and others in the testicle (*Parenchym-zellen*). They were rarely found in the mamma of the virgin. Von Brunn would also connect them in some way with the secreting cells.

entitled to the support that arises out of a generalisation on the whole well established.

We come now to the later stage of evolution, immediately preceding the actual formation of milk. Fig. 17 is a drawing which might have been made from any part of the mammæ of cats that were pregnant with fœtuses almost full grown. The same appearance might also have been drawn from many parts of the udder of a ewe that was pregnant with a fœtus about a foot long. At the stage of evolution, the description of which we have now reached, the glands are voluminous, and of the almost uniform parenchymatous consistence of the fully expanded

Fig. 17.



From the mamma of a cat pregnant with fœtuses almost full grown. Vacuolation of the epithelium; two acini on the left containing mucus. Magnified 300 diameters.

state. In the case of the ewe just mentioned, a clear brownish fluid could be expressed from the teats. On microscopic examination, the lobules are fully expanded, and the interlobular tissue forms quite thin septa. The entire field of the microscope is occupied by the closely-packed acini, which are of the full size. The appearance that is characteristic of this stage is given in Fig. 17. Many acini are filled with a mucous fluid, colouring with the staining agent, and often penetrated with a large number of vesicles. The floor of the acinus, and the circumference of it when seen in profile, are occupied by a complete set of cells in regular order, all of which are vacuolated, and most of them

in exactly the same manner. If the figure is referred to, it will be seen that the peripheral mass of the vacuolated cell is almost always large; it has a somewhat oblong or reniform shape, and shows a nucleolus. Looking at the floor of an acinus, an impression is got which it has been found difficult to convey in the drawing. The excentric nuclear bodies all look not so much as if they were situated on the periphery of a round vacuole, as that they lay each on one side of the polygonal meshes of the basement membrane. This simply re-opens the former question of the relation between the polyhedric form or outline of the cell, and the regular polygonal space in the basement membrane in which it is set. But if the profile view of the epithelium is looked at, it becomes clear that we have to deal with the same vacuolation as elsewhere; and the peculiar appearance of the floor of the acinus must be owing to the prominence of the fibres of the basement membrane, side by side with the delicate vacuolar outlines. The mucous fluid in the cavities of the acini is obviously the vacuolar product of the epithelium, and it is interesting to note that the period at which mucus was found in the acini in the course of involution, corresponded to exactly the same degree of vacuolation of the cells. It is the period of involution that is represented in Figs. 5, 6 and 9, the two former being from a cat nine days after the end of lactation, and the latter from a sheep that was killed three weeks after parturition, without having been milked.

It is a somewhat remarkable circumstance that the case of the ewe with a fœtus about a foot long, and therefore far advanced in pregnancy, shows in some places exactly the same enormous collection of small round cells about the acini as in the case of the ewe in the involution process from which Fig. 9 is taken. In both cases the small round cells are, in isolated portions of the gland, so numerous as to completely obscure the outlines of the acini. There is, no doubt, something unusual in the circumstances of each case; but they none the less illustrate the physiological law of their respective processes, and the remarkable parallelism between the same[1]. In the cases of advanced evolution in the cat, as repre-

[1] In the one case, the ewe was kept at the Brown Institution, London, among others that were used for the experimental study of sheep-pox, but it was not itself inoculated. It died from some unknown cause (probably sheep-pox acquired in the

sented by Fig. 17, there is little or no appearance of cellular waste products outside the acini, and within the acini it is only the fluid product that is to be seen. Whether the cellular masses that occupy the periphery of the vacuoles in this stage are ever disengaged and thrown off as cellular waste, or whether the cell as now seen is only partially vacuolated but destined to be entirely so, is not easy to decide. It is certain that there are found side by side with those signet-ring like cells, a few that are nothing but delicate ring-like forms, without any cellular enlargement on their periphery. Again, if there is any cellular waste at this stage of evolution, it would be discharged by the ducts, along with the mucous or fluid products of the epithelium.

There is but a single step from the period of evolution just described to the perfect state of the epithelial cell which is found a day or two before parturition. The appearance of a mosaic of polyhedric cells with a central nucleus may be seen in occasional acini of the previous stage, but the protoplasm of the cell is perfectly hyaline and not at all granular; the nucleus seems rather to lie in the centre of an empty polygonal space. About the time of parturition the epithelium has acquired its granular appearance, and shortly after the birth of the offspring the milk begins to be formed in great abundance. The milk of the first few days contains a large number of the well-known colostrum cells, which are the last of the long series of imperfect secretory products that have been thrown off during the evolution process. The appearance of well-defined colostrum cells is very much the same as that of the cells in Fig. 8, which are found within the acini in the earliest stage of the involution of the gland.

The method followed in the account of the involution process, of giving a description of the gland at various well-marked stages of its progress, without any commentary as to the physiological significance of the same, has been mainly followed also in the account of the evolution; and if it be added, that the well-marked stages that have been chosen for description are of necessity some-

ordinary way of contagion); the lungs were full of a whitish material, and the uterus contained two nearly full-grown lambs that had been dead some days. The other ewe was inoculated with sheep-pox on Dec. 8th; it recovered completely, and was killed on March 13th, having given birth on Feb. 26th to a dead lamb full grown.

what conventionally divided from each other, the preceding account of evolution may be taken as a fairly complete statement of the facts of the case. It now remains, as in the chapter on involution, to consider, by way of summary, what is the physiological law of the gland's activity during the restoration of its structure.

It has been explained, in the first chapter, that it took several weeks for the secretory activity of the mamma to run down or to subside, that the gradual subsidence was accompanied with the production from the epithelium of a good deal of cellular waste, and that the conclusion of the process of involution left the gland with all the parts of its framework entire, but with the acini greatly contracted and containing only a heap of nuclear cells. The renewal of the gland's activity begins, roughly speaking, with the commencement of the next pregnancy, and it brings with it, step by step, the restoration of the full epithelial structure which had been lost during the previous subsidence. This rehabilitation is in most animals a very slow process; one may say that it is unnecessarily slow, in respect of the object to be attained. But, as a matter of fact, it is not completed till the term of gestation is at an end. The evolution of the gland is, as it were, distributed over the entire period of pregnancy. Starting then with the resting state of the gland, we are met with the question, How do the nuclear cells that are left occupying the acini at the end of involution assume the character of nucleated polyhedric epithelium, and according to what law of cellular activity does this renewal take place? Now, as was contended *mutatis mutandis* in the analogous case of involution, it is not to be supposed that the particular set of nuclear cells with which an acinus is furnished when the unfolding process begins are the same that, after various transformations, spread over a very long period, become the polyhedric epithelium of the lactation stage. On the contrary, there is no more certain fact in the study of the periodical mammary evolution than the large production from the acini of various kinds of waste-cells at various stages of the process; the figure No. 14 is well adapted to show a large collection of cells that have been thrown off from the gland. It is in the successive renewals of the cells within the acini, which this fact involves, that we find the successive steps towards perfect epithelium. Each new generation of cells is more like the polyhedric nucleated epithelium than the

preceding. One knows no process of simple multiplication of cells by which the nuclear elements of the resting state could produce polyhedric epithelium, even if the process were continued through many generations. If they multiplied, as no doubt they do, they would produce nuclear cells like themselves; and if we were limited, in our explanation, to a mere process of proliferation or a formative process, it would be impossible to understand how those nuclear cells ever came to have such descendants as the perfect epithelial cells. But we have already seen that the activity of the mamma is always double; there is both a formative action and a functional action, and those two, in health, always go hand in hand. Therefore, when the re-awakening forces of the breast are directed to the cells within the acini, the latter not only multiply, but they are at the same time transformed in the direction of the secretion. It is the transforming force and the increasing intensity of the same that is the factor wanting to explain how the nuclear cells at one end of the scale are the progenitors of elements so unlike themselves as the perfect epithelial cells at the other end. The unfolding of the apparatus of secretion is necessary to the revival of the function, and, on the other hand, the return of the cells to their perfect form could not take place were it not for the increasing intensity of the secretory force. This is the dualism of structure and function, the highest correlation in our knowledge of the organism, the double name of "two things mutually explaining and equally real." The dualism of structure and function is therefore not to be resolved into terms more ultimate, and it is in that sense inexplicable. But it is at least an illustration of the union between structure and function to point out that the one varies as the other varies; that a low degree of function resides in what may be called a crude shape of cell, that a high degree of function resides in what may be called a perfect shape of cell, and that the intensifying of the function and the perfecting of the cell go hand in hand.

The restoration of the resting cell of the acinus to its polyhedric epithelial shape does not take place in one generation of cells, but in the course of several generations; the intermediate generations of cells are, from the other point of view, the waste products of the crude secretion. The earliest change noticeable in the unfolding of the breast is the presence within the acini of a

limited number of large yellow granular cells. Those cells were, in the former chapter, found to be the last products of the declining secretory force in the upfolding process of the gland, they are the first products of its re-awakening in evolution; and it will be shown in the pathological part of the work, that the same transformation of the epithelium is the characteristic effect of any feeble stimulus whatever, applied to a gland in the resting state.

The first step then in the periodical evolution of the gland is the transformation of nuclear cells of the resting state into large granular cells containing yellow pigment. But not all the cells of an acinus, or at any rate not all of them at once, assume the enlarged and pigmented character. Just as we saw that some at least of the resting cells of the acini were derived from the large yellow granular cells of involution by the latter losing their pigmented granular substance and leaving their nuclei behind them, so it now appears that certain of the same nuclear resting cells recommence the cycle of change by acquiring a granular and pigmented investment. In some such way, at least, must one construe the re-appearance within the acini of the large pigmented cell in the early stage of evolution. The change from a nuclear to a large granular condition is observed elsewhere in the adult body; Virchow in particular has remarked on the reality of this change. Combating the mistake which, as he says, is commonly made of treating white-blood corpuscles, lymph-corpuscles, and the cells of the follicular tissue of lymphatic glands as if there were no morphological differences between them, and as if they were identical, he points out that there is a distinct act of transformation before one of these can become the other, and that this transformation is no less real than the passage of a cell of the *rete mucosum* to become an epidermic cell. For example, the commonest kind of cell in the parenchyma or follicular tissue of a lymphatic gland is a "naked" nucleus, without an obvious cell-body. The cells of the lymph, on the other hand, have a more voluminous cell-body, which is also so much more dense that the nuclei become less distinct. Still more is this the case with the colourless blood-corpuscles, whose dense and exceedingly granular bodies quite conceal their nuclei, so that the latter are made visible only by reagents[1].

[1] *Cellular-Pathologie*, 4th edition, pp. 210—212.

That is no doubt an analogous change under somewhat different circumstances. In the embryonic development there is hardly a tissue of the body but would show similar changes in its cells, as they pass from their indifferent nuclear form to their characteristic mature form. In the present case the increase in size is both very great and apparently very sudden, and the swollen cell-substance is occupied by yellow pigment. I have already mentioned that only one or two cells in an acinus at one time appear to be subject to the reviving secretory force, and that the large yellow cell often includes more than one nucleus.

The pigmented cells are thrown off from the acini in large numbers; in the case from which Fig. 14 has been drawn, a large collection of them had been accidentally formed in the fat-tissue just outside the secreting structure. It is probable that they escape from the acini by passing through their walls, the still upfolded acini being not yet in free communication with the lumen of the ducts[1]. If that collection be examined with a higher power, it would be found that some of the cells have two nuclei, that the nuclei are all excentric and therefore clearly to be seen, and that a cell here and there has undergone the typical vacuolation, the fluid in its vacuole being of the same yellow colour as the granular cell-substance of the others. The pigmentation does not continue into the later stages of evolution, just as it did not commence till towards the end of involution. As the functional stimulus gets gradually stronger, the cells that are produced within the acini, whatever more epithelial form they may have attained to for a brief space on the acinus wall, are thrown off as somewhat large nuclear bodies of a granular appearance, which often acquire an elongated or spindle form in their passage through the interfascicular spaces. The difference between them and the pigmented class of products, is that they have undergone a certain amount of functional transformation within the acini, as is shown by the presence of a sometimes granular and sometimes fluid material in the acinous cavities;

[1] Astley Cooper (*Anatomy of the Breast*), using the now obsolete names for glandular structures, says: "In the fulness of lactation, those leaves [lobules] are full of cells [acini], which can be readily injected and demonstrated; but at other periods they do not admit of being filled, and a most minute injection may then be made of the lactiferous tubes, yet no cells [acini] appear."

whereas the large granular pigmented cells are thrown off unchanged. It may be recalled to mind once more that the pigmented cells do show a tendency to become vacuolated, and otherwise to lose their cell-substance after they have left their proper functional habitat.

Coming to the last stages of evolution, we again reach familiar ground. In the glands corresponding to almost the full size of the fœtus, there is perfectly typical vacuolation of the epithelium going on, with the formation of mucus as the fluid product; and that vacuolation takes place in cells that have now recovered the polyhedric form of epithelium. By this time the secretory excitation of the gland has increased so much in intensity that the functional transformation is only slightly different from that of the perfect state. Those slight differences are however instructive. They enable us to interpret aright the nature of the secretory process when the function is at its height, and when the transformation of the epithelium has no morphological features; and they equally help to clear up the obscurities of the process in its earliest stage. The parallelism with the involution process is complete. We again find ourselves to be following a progressive series of vacuolation changes, with a correlation between the fluid and cellular elements of the vacuolation. At one end of the series, everything is vacuole, and there is no cellular production; at the other end of the series, everything is solid or cellular, and there is no vacuole. The glandular activity in its re-establishment, no less than in its subsidence, follows the law of endogenous cell-formation, and that is also the law of its action when it is in its full career. Again, the periodic evolution is accompanied by much cellular waste; and the cellular waste of the evolution is more than that of the involution, in proportion as the former process is spread over a longer period.

CHAPTER III.

THE LYMPHATIC GLANDS OF THE BREAST IN CONNEXION WITH THE DISPOSAL OF ITS CELLULAR WASTE.

THE main physiological conclusions of the two preceding chapters may be said to be the performance of the mammary function according to the law of endogenous cell-formation, and the production, during involution and evolution, of a large amount of cellular waste, arising from the operation of that law in the subsiding or immature periods of the function. Of those two conclusions, one may be said to be more theoretical and the other more practical; if the theoretical conclusion be held in doubt, the facts relating to the waste-cells may be taken without theory. The present chapter will be devoted to a consideration of the further progress and ultimate disposal of the waste-cells in the lymphatic glands.

It is necessary, at the outset, to recapitulate the various forms of cells thrown off at different periods. They may be classed in three groups, subject always to the reservation that there is a gradual transition between them. The first kind of waste products are the familiar colostrum cells, which approach most nearly, whether at the beginning of involution or the end of evolution, to the perfect secreting cell. The second kind are the more or less nuclear bodies of somewhat various shapes, which are the survivals of well-marked vacuolation of the epithelium and are usually associated with a mucous fluid; they characterise the middle period of both processes. The third kind are the very remarkable large pigmented cells, which are the latest products in involution and the earliest in evolution.

The disposal of the colostrum cells at the end of evolution (beginning of lactation) is a matter of common observation. They are got rid of by the ordinary outlets of the secretion, viz. the ducts, and they are found mixed with the first milk in large numbers. The corresponding imperfect products at the close of lactation are no doubt disposed of in the same way, although their discharge is not accelerated, as in the former case, by the strong flow of the rising secretion. The ducts are, however, found for several days after lactation, and even as late as the second week, to be filled with a milky substance, and in some cases a fluid escapes from the breasts for a considerable time after weaning. The later or non-vesiculated kinds of waste-cells are got rid of usually in a different way. Preparations have already been described and figured which show them to be collected about the acini and in the fibrillar tissue. The acini, at the periods when those cells are produced, do not appear to communicate freely with the ducts; the cells therefore find their way into the lymphatic channels of the gland, whence they are in health ultimately drained off. All the waste-cells of the cruder sort, though they differ among themselves in size and in other respects, may be classed together for the present purpose. But, as might be surmised, it is the pigmented cells that are again the least doubtful sources of evidence, and they will be made to sustain the proof of the statements that apply to both kinds alike. They are perhaps not the most abundant of the waste-cells, but their unmistakeable yellow colour makes them by far the most valuable for demonstration, and enables the whole question of the disposal of the cellular waste to be treated much more objectively and briefly than it could otherwise be.

Now, as regards the large yellow granular cells, they are most commonly found outside the acini in the position given in Fig. 10. Having once entered the lymphatic spaces, they for the most part continue their progress in the same. But a case has already been described and figured which constitutes an exception to the general rule. In it the yellow cells are also found to have escaped through the walls of the acini, but they travel along the submucous tissue of the ducts, and at convenient points break through into the latter, which were found throughout the gland to be filled with them. Apart from this case, there is the

clearest evidence, collected from a large number of preparations, that the pigmented cells are conveyed directly from the mamma to lymphatic glands situated, in the animals enumerated, at each end of the mammary chain. Those at the upper end are the axillary glands; those at the other end are the glands more particularly referred to in the sequel, and they require a few words of description.

It has been already mentioned that the inguinal portions of the mamma rest on cushions of fat, which are sometimes of great thickness. Thus, in two cases of advanced involution, in the dog and the cat, the lower end of the mammary chain, forming a thin layer of tough substance, rested on a cushion of fat about three-fourths of an inch thick. In each of the cases there were found in the centre of the fat one or two quite small masses of tissue, which proved on examination to be lymphatic glands. In most of the other cases the lymphatic glands have been found of larger size, and placed close to the under surface of the mamma and towards its outer border, where also the fat extends. Sometimes a chain of them is found extending beneath the mamma for two inches or more forwards along the abdominal wall, and these also are embedded in a certain quantity of fat. They are for the most part long, narrow, and flattened cylindrical bodies, with a hilus extending along the whole length of one edge. The appearance of a hilus is produced by the apposition of two rounded borders, as if the gland had originally been a flat disc-shaped body like the spleen, and had become folded upon itself. Along the hilus border there are always found the cut ends of an artery and a vein of considerable size.

From their position, these lymphatic glands seemed to belong to the mamma in some especial way. They were found to vary much in size in the different cases, but it has not been possible to make out that they vary in any exact measure with the periodical changes in the mamma itself. However, their relation to the mamma is put beyond question even by a superficial inspection. One particular case out of a large number is singularly adapted for demonstration, and it will be briefly described. It occurred in a bitch that had a large tumour occupying a certain limited portion of the mammary chain on one side. The animal was killed, owing to the incurable nature of the disease (secondary

tumours in the liver and lung), and the whole chain of glands on both sides was dissected off. The new growth was perfectly circumscribed; and the entire mamma on one side and the greater portion of it on the other were found to have the usual tough fibrous appearance of the gland at or about the resting state, although with an unusual amount of yellowish-brown pigmentation. The attention is specially directed to the inguinal portion of the gland on one side. It had the appearance, as has been said, of a tolerably normal mamma at or near the resting state; it was about a line in thickness and lay upon a cushion of fat half an inch thick. In the midst of this fat and at a distance of about one-quarter of an inch or more from the under surface of the gland, there were found two quite small parenchymatous bodies of a uniform yellowish-brown colour, which proved on microscopic examination to be lymphatic glands. One of them appeared as the cross section of a slightly curved disc-shaped mass, and close to its concave surface there appeared the cut ends of two large vessels. The other was a somewhat pear-shaped body placed in the fat in an oblique position.

The microscopic examination, as has been said, showed them to be lymphatic glands. But they did not contain the relative proportions of the various tissues that are ordinarily met with in lymphatic glands. The follicular tissue corresponded chiefly to the thick end of the pear-shaped mass and to the convex surface of the crescentic; the cells of that tissue were of the ordinary lymphoid kind. The surface of the follicles was very commonly strewn with grains of brown pigment; otherwise the follicular tissue was not pigmented. Probably the greater part of the glands consisted of the wide lymph-sinuses and the dense fibrillar tissue of the hilus, through which the former penetrated. The large lymph-sinuses were everywhere filled with the yellow granular cells that have been described and figured in the first and second chapters. Fig. 20, on a subsequent page, is a drawing of a portion of one of these preparations; the enormous preponderance of the stroma of the hilus and of the lymph-sinuses, and the quite rudimentary condition of the follicular tissue, will be at once apparent, but the further description of the preparation is reserved till later. The yellow cells are represented in the woodcut simply as granular.

It has been already mentioned that the mamma of this case was to the naked eye more pigmented than usual; and on microscopic examination many yellow or brown granular cells were found in and around the acini, which were for the most part only a little larger than in the resting state. A series of sections were made which included in one piece the mamma, the fat beneath it, and the lymphatic gland in the midst of the latter; and it was possible, in one and the same preparation, to identify in the clearest manner the pigmented cells of the mammary acini with those in the lymph sinuses of the lymphatic gland. Certain tracts of tissue were found running through the fat between the mamma and the lymphatic gland, which contained, no doubt, the collapsed lymphatic vessels. None of the pigmented cells were found at any point between the mamma and the lymphatic gland, and that circumstance will now be in a manner explained by reference to a preparation from another case. It is a case that has been already referred to, and from which the figure on page 43 has been drawn. It represents the early stage of evolution in the mamma of the cat, the fœtuses having been $2\frac{1}{2}$ inches long. The acini and surrounding tissue contained numerous large pigmented cells, and so also did the lymphatic glands of this case, a drawing from which latter is introduced afterwards (Fig. 19). But the remarkable feature of the case is the collection of the same yellow cells in the fat tissue outside the mamma. It seemed at first sight as if this were a case of the pigmented cells on their way through the submammary fat to the lymphatic gland. But a second examination showed that such was not the case. In the inguinal mamma of this case, as in one or two others, there was, in addition to the fat beneath the mamma, a small quantity of fat on its upper surface. Fat on the upper surface is unusual in animals that have the extended chain of glands; for the mamma, or its loose fibrous investment, nearly always adheres closely to the skin above. Now, on a second examination of the preparations, it proved to be the external layer of fat, and not the cushion beneath the gland, that contained the large collection of yellow cells. It is not at all a fanciful account of the matter to say that the pigmented waste-cells had made their escape from the secreting acini on the wrong side of the organ; they had travelled along

channels that were no doubt open to them, but which led into a layer of fat that had no further outlet. The unusual layer of fat on the upper surface of the gland acted as a trap to a certain number of waste-cells; if they had been conveyed like the others into the fat on the lower surface, they would have been on the way to their proper reservoir, the lymphatic gland. The detention of waste-cells in the fat in this case is of the exceptional kind that proves the rule; if there had been no obstacle to their transit they would have passed singly and quickly through the lymphatic channels, so that the preparations of the animal killed at a particular moment would probably not have shown a single cell in its passage. The same difficulty of finding cells in some particular act of their life constantly occurs in the histology of the dead tissues. In histological investigation mere traces or indications of a cellular process must often suffice as the basis of a general conclusion for which they seem inadequate. The reasonableness of the conclusion depends very much on the support that it receives from associated circumstances. In the present case the evidence amounts as nearly as possible to demonstration; the granular pigmented cells, in one and the same preparation, are found within the secreting acini, in the connective-tissue spaces outside the secreting structure, and in the lymph-spaces of the subjacent lymphatic gland. In some cases there has been observed also a collection of cells in the tissue just outside the convex surface of the lymphatic gland; that is to say, at the points where the in-carrying lymphatic vessels enter. But in those cases the cells were not of the pigmented kind, and their occurrence might be explained in some other way.

So far as the facts have been already stated, the lymphatic glands under the mamma are to be viewed as special appendages of the secreting organ; whatever other function they may have, they are obviously there to receive the cellular waste products of the secreting gland to which they are attached. In the case described, where the lymphatic gland consisted to a great extent of lymph-sinuses filled with the pigmented cells from the mamma, it was impossible to resist the notion that the collection of the cellular waste of the secretion and the disposal of the same was its *raison d'être*. Whether all the lymphatic glands in the body

participate in this function for the tissues, secreting and other, with which they are connected respectively, is a question that lies entirely outside the present inquiry. I am bound, however, to mention a particular case of the same pigmentation in lymphatic glands other than those connected with the mamma. In the case of a cat that proved to have completed the involution process, there were the usual evidences of pigmentation in the mammæ. The lymphatic glands beneath the inguinal mamma were all streaked on the surface with several yellow lines, just as the mesentric glands at a certain stage of digestion are streaked with white lines owing to the presence of chyle in their afferent vessels. The axillary glands were streaked in the same way. The presence of pigment in both sets of lymphatic glands was capable of explanation by reference to the state of the mamma. But it was found, on examining the animal further, that there was a chain of lumbar lymphatic glands lying along the lower end of the aorta which were streaked on the surface in exactly the same manner. This was at first inexplicable, and threatened to upset altogether the theory of a special relation between the mamma and the lymphatic glands near it. But an explanation was forthcoming on continuing the dissection. On cutting open the uterus, the mucous membrane over a small area in both its horns, about half an inch from the cervix on each side, was seen to have a yellowish colour. On making a transverse cut at those points, a distinct deposit of a yellow substance was seen in the sub-mucosa, and the microscope showed this to be a collection of yellowish-brown pigment grains strewn among the sub-mucous tissue, but not associated with any cell-forms. Here then was an organ, known to be associated with the lumbar lymphatic glands, which contained traces of pigment-formation in its tissue, and which had probably been the source at an earlier period of the very much larger amount of pigment represented by the pigmented cells in the afferent lymphatics and sinuses of the lumbar glands. The pigmentation of the various sets of lymphatic glands, portal and mesentric, bronchial, and others, is in all probability to be explained in a special way for each of the sets. The pigmentation of the mammary lymphatic glands may be treated of by itself, all the more so as the pigment is brought to them beyond doubt in the substance

of cells that do not belong to the ordinary circulating cells of the lymph.

The lines or streaks of pigmentation on the surface of the lymphatic glands in the case just referred to evidently corresponded to the cortical lymph-sinuses, with which the in-carrying lymphatic vessels are in direct connexion. In the microscopic section the lymph-sinuses of the cortex are sometimes found packed with the mammary pigmented cells, arranged in rows and compressed into a more cubical form. From the cortical sinuses they pass, like the lymph, into the centre of the gland. Their progress therein, and the changes that await them, have now to be traced. This part of the investigation, relating in the first instance to the disposal of the cellular bye-products of the mammary secretion, will be found to have a bearing on

The general Plan of Structure and the Function of Lymphatic Glands.

The minute structure of lymphatic glands has been studied by so many observers during recent years that there is little room to add anything to the histological details. But there need be less hesitation about offering a re-interpretation of certain of those appearances; while the whole question of the function of lymphatic glands is open to elucidation even of an elementary kind. As regards structure, the lymphatic glands consist of three kinds of tissue, which are represented in Fig. 19. The first and most abundant is the follicular, which includes both the round or pear-shaped follicles proper, occupying the cortex of the gland, and the cylindrical continuations of the same which occupy the medullary part of the gland. The follicular tissue consists of dense masses of small lymphoid cells, which lie in the meshes of a fine network that can be made visible by shaking the cells out of it. There is no difference between the cortical follicles and the medullary cylinders as regards minute structure. The second class of structures are the lymph-sinuses. They accompany the follicular tissue throughout the entire gland, forming somewhat narrow spaces around the follicles at the cortex, but widening towards the medulla

into spaces round the cylinders of lymphoid cells, which are often as broad as the cylinders themselves. The lymph-sinuses are not perfectly open and empty spaces. On the contrary, they are crossed in all directions by a network of bands or fibres, and they are always found more or less filled by cells. But if they are compared with the follicular tissue in this respect, the branching fibres within them do not form at all so close a reticulum, nor are the cells that lie among the fibres so numerous or so densely packed. The lymph-sinuses, even when filled with cells, have a much lighter appearance than the follicles or cylinders, and they are spoken of by Recklinghausen as the "*lichtere Stellen*[1]." The same writer also points out that the cells in the lymph-sinuses are only temporary occupants. The third kind of structure within the gland is the trabecular, of which His makes a subdivision under the name of "stroma of the hilus[2]." The trabecular tissue is of a densely fibrillar kind, and forms the capsule of the gland at one pole, the stroma of the hilus at the other, and the true trabeculæ or framework of the gland at all intervening points. The trabeculæ are related to the other structures of the gland in the manner shown in Fig. 19; they divide two lymph-sinuses from each other; the fibres that are stretched across the lymph-sinus are attached to the follicle or cylinder on the one side of the space, and to the trabecula on the other. It is now very generally admitted that the trabecular tissue, including that of the capsule, contains a certain quantity of involuntary muscular fibre in its substance. The assertion was first made by Malpighi, on what grounds it is not known[3]. It has been re-affirmed of recent years by Brücke, Heyfelder, His and others on various grounds, such as the isolation by means of nitric acid of highly characteristic muscular fibres, with rod-shaped nuclei, and the frequent occurrence of rod-shaped nuclei *in situ* throughout the substance of the trabeculæ. Frey is of opinion that the latter cannot be distinguished from young or embryonic connective-tissue cells. W. Müller, after reviewing all the circumstances, thinks the existence of muscular fibres in the trabeculæ to be probable, but he rests

[1] *Stricker's Handbuch*, p. 241.
[2] *Untersuchungen ueber den Bau der Lymphdrüsen*, Leipzig, 1861.
[3] His, *loc. cit.*

his opinion less on the completeness of the histological evidence than on the fact made out by Brücke and Heyfelder that the lymphatic glands of animals can be made to contract by an electrical stimulus[1].

As regards the circulation through the gland, the afferent lymphatic vessels are known to discharge themselves into the lymph-sinuses at various parts of the cortex, and the outcarrying lymphatic vessels to take origin from the wide lymph-sinuses in the hilus. The following account of the blood-vascular distribution is given by His. Several arterial trunks enter at the hilus; in the stroma of the hilus takes place the coarser branching; certain of the branches pass into the trabeculæ; but the greater number of them pass into the medullary cylinders and run in these towards the periphery into the follicles. The vessel running in the axis of the cylinder gives off many fine branches which open into a capillary network spread out on the surface of the cylinder. Out of this capillary network several small venous branches take origin, which return to the hilus by a venous trunk running along the axis of the cylinder and lying side by side with the artery therein. As to the follicles, they receive their chief arterial supply by extension of the vessels running in the cylinders, and the capillary distribution and venous reflux is on precisely the same system as in the cylinders. In both cases the greatest capillary distribution is on the rounded surface which is directly exposed to the lymph-sinus. The lymph-sinuses contain no blood-vessels.

The most recent additions to the histology of the lymphatic glands concern the lymph-sinuses and their contents. The branching fibres that stretch across the sinuses from the follicle or cylinder on one side to the capsule or trabecula on the other have been usually described as branched connective-tissue cells or spindle-cells containing nuclei. From another point of view all the nuclear cells that are seen in the lymph-sinus have been divided into two classes, those that lie free in the meshes of the reticulum (the lymph-cells) and those that are the fixed cells of the reticulum. Fully accepting the distinction between the two kinds of cells, Bizzozero[2] has endeavoured to show that the latter are not really branching connective-tissue cells, but that they lie upon the fibres

1 *Henle und Pfeufer's Zeitschrift*, 1863, p. 121.
2 *Moleschott's Untersuchungen*, Vol. XI. p. 300.

of the reticulum in one or other of two ways: the cells of the reticulum are either thrown round about the fibres, enclosing them as if in a tube of protoplasm, or they are stretched across an entire mesh of the reticulum, like a window-pane in its frame. In the former case the nucleus is seen to lie on the side of the fibre, in the latter case it has a central position in the cell, as in a front view of an endothelial cell. About the same time that Bizzozero made these observations, Ranvier was also led to a somewhat similar conclusion. In sections of lymphatic glands hardened in picric acid solution, he was able to obtain, according to the time of immersion in the solution, either the reticulum without a single cellular element in or upon it, or the reticulum and its branches covered by endothelial cells. He concluded that the reticulum is not formed of branching cells joined together by their processes, but that it is formed of fibres of the connective-tissue united in a network and covered by endothelial cells[1]. It remains to be added that W. Müller had observed the fixed elements of the reticulum to be of two kinds, mature and embryonic. The one were in the form of thin connective-tissue fibres with spindle-shaped nuclei; the other consisted of a delicate finely granular ground-substance (protoplasm), branching into a network, and with elliptical nuclei embedded in it. Along with the elliptical nuclei there could be observed other and smaller cells which represented all transition stages to the mature lymph-corpuscles. Between the numerous irregular openings of this network the lymph-current passed, as if, to quote the apt expression of Brücke, through the pores of a sponge[2]. It has also been observed by Toldt that some fibres of the reticulum were nucleated, while others were simply thread-like filaments[3].

Notwithstanding the numerous histological researches on the lymphatic glands, their functional import remains conjectural, and in particular the elaborate filtering apparatus which is formed by the branching fibres or protoplasmic bands stretched across the lymph-sinuses has had no adequate use assigned to it. The observation of Leydig, to the effect that "the production (*Erzeugung*) of lymph-corpuscles is the special physiological task of lymphatic

[1] See his *Traité Technique d'Histologie*, p. 398.

[2] W. Müller, *loc. cit.* 126—128.

[3] Eine Methode zur Injection der Lymphbahnen in den Lymphdrüsen. *Sitzungsberichte der Wiener Akademie*, Jan. und Feb. 1868.

glands[1]," sums up pretty nearly the view that still prevails. In addition to contributing to the number of lymph-corpuscles (white blood-corpuscles), the lymphatic gland is supposed to purify the lymph in its course through it. Thus, Virchow points out that there is no free passage for the lymph through the gland; it must pass between cells more or less closely packed together. The cells of the gland are like the particles of a charcoal filter; the lymph percolates through them and wells out on the other side "as it were filtered and purified[2]." But it need not be pointed out that this is only a graphic illustration, which leaves our intimate knowledge very much where it was before. A circumstantial account of the physiological mechanism of the gland is given by His. The lymph entering the gland by the afferent lymphatics circulates under low pressure in the lymph-sinuses and moves slowly therein towards the hilus. The pressure is insufficient to drive the lymph from the lymph-sinus into the gland-substance. On the other hand, the blood-pressure will cause a stream to flow from the highly vascular gland-substance outwards to the sinus, and this stream will carry with it, along with the fluid transuded from the capillaries, a number of the lymphoid cells that are being constantly reproduced in the gland-substance, and so convey them to the lymph-stream. With the contraction of the capsule and trabeculæ, (a rythmical contraction depending on the presence of involuntary muscular fibres in them,) the whole gland seeks to diminish in size, and as the afferent lymphatic vessels possess valves to check a reflux, the lymph-sinuses will empty themselves into the outcarrying lymphatic vessels. At the same time, in consequence of this contractile pressure, the gland-substance will for the moment contain less blood. As soon, however, as the contraction ceases, it must happen, in consequence of the sudden relaxation of tension in the interior of the gland, not only that the gland-substance will become again richer in blood, but also that the emptied lymph-sinuses will again become full. The re-filling of the lymph-sinuses may take place both from the afferent lymphatics and from the gland-substance; if the afferent lymphatics contain no lymph, then the lymph-sinuses are filled entirely by the fluid that has transuded from the gland-substance[3]. One function of the lymphatic glands

[1] *Lehrbuch der Histologie*, 1857. [2] *Cellular-Pathologie*, p. 208.

[3] *Loc. cit.* p. 21.

appears then to be that of adding to the lymph-corpuscles of the circulating fluid a certain number more of the same kind derived from the follicular tissue of the gland. Recklinghausen observes that the multiplication of lymphoid cells in the follicles has in fact never been seen, but that it is indirectly probable for several reasons, the chief of these being that the lymph leaving the gland contains more corpuscles than the lymph entering it.

Returning to the material of this research, there are introduced factors of a new order altogether, which may or may not be special to the lymphatic glands of the mamma. We have to deal with the conveyance to the lymphatic gland of a peculiar class of cells, which are waste products of the secreting gland; and we are concerned not so much with the production of actual new cells within the lymphatic gland, as with the changes that it effects upon a certain quantity of crude cellular material supplied to it from without. Now, it is in this altered stating of the problem that we may find some light thrown not only on the function of lymphatic glands but also on their structure. It has been already mentioned that the large yellow granular cells which are produced within the mammary acini in certain states of the function, and are often to be seen in the tissues outside, are also found in the lymph-sinuses of the lymphatic gland. It is not impossible that an objection may here be taken as to the actual identity of the cells found in the two situations. It may be said, for instance, that the large yellow cells lose their pigment within the gland, as no doubt they sometimes do, and that the pigment-granules are taken up by the ordinary lymph-corpuscles that come in contact with them, and so get conveyed to the lymphatic gland. It is not unreasonable to suppose that some such explanation may apply to the pigmentation of lymphatic glands in other situations, especially where the pigment seems to come from red blood-corpuscles. But in the case of the mammary lymphatic glands, there can be no doubt that the large yellow cells that originate in the secreting structure pass bodily into the lymphatic gland. Entire cells, more than twice the size of lymph-cells, are found in the lymph-sinuses, and the collections of them in the lymph-sinuses have often a close resemblance to the collections of the same cells in the interlobular tissue. But in the lymph-sinuses the pigmented cells of

the mamma begin to undergo changes of form and reductions in size, whereby their identity becomes lost.

When a somewhat loosely packed lymph-sinus is examined in one of the pigmented mammary lymph-glands, it becomes at once apparent that the pigmented waste-cells *occupy the place of the branched cells of the reticulum;* their nuclei are the nuclei of the reticulum, and their pigmented bodies and processes lie upon the expansions or branchings of the same. Fig. 18 on a later page is a representation of this appearance. There are to be seen in the reticulum no other cells or nuclei but the pigmented cells and their nuclei; the only other elements of the reticulum are the fibres. These are fixed structures in the lymph-sinuses, and in the preparations that are now being described they appear to be the only fixed structures. I am, however, not in a position to deny the existence of the endothelial cells described by Ranvier, which require special methods of preparation to make them visible. At the same time, if all the cells of the reticulum can be equally dislodged, it seems to me somewhat arbitrary, in the absence of very specific differences, to describe some of them as endothelial cells and others as cells belonging to the circulating lymph; and as regards the cells described by Bizzozero, cells that were wrapped round the fibres like a sheath of protoplasm, or that stretched across the meshes like the panes of glass in a window, I have no doubt that they correspond to the pigmented cells that I now describe, and that they belong to the circulating cells. The real distinction among the cells in a lymph-sinus is that some of them adhere more closely than others to the fibres of the reticulum; and the significance of those differences among the pigmented waste-cells has now to be considered.

Many of the large yellow granular cells in the lymph-sinus are of their usual round form; but many of them—and in the emptier lymph-sinuses the whole of them—are either drawn out into processes which follow the direction of the fibres, or they are otherwise stripped of their protoplasmic cell-substance and their pigment, in all degrees down to the condition of naked nuclei. The various steps of the process by which the cells lose their protoplasm and their pigment in the meshes of the reticulum are so clear that the fact in its entirety becomes well established. For example, a large yellow granular cell with visible nucleus has its substance

drawn out into two or three or four processes which correspond to the direction of fibres passing across the sinus. Again, a row of free pigment-granules is seen to be the continuation of a somewhat truncated cell-process, the granules lying in or upon the fibre. Again, the pigmented cell is found stripped of all its cell-substance except a mere yellow fringe round the nucleus. Lastly, from another point of view, nuclei are constantly met with which have a few granules of yellow pigment clinging to them. One might multiply indefinitely such examples of transition appearances in the large pigmented cells while they are in the course of losing their pigmented cell-body.

The next question that arises is the manner in which the denudation takes place, or the part that the so-called fibres of the reticulum play in the same. Reference has been made to the distinction by W. Müller of two kinds of substance occurring as the reticular meshwork. One kind he describes as the ordinary connective-tissue bundles containing the ordinary spindle-cells; the other kind was a finely granular protoplasmic substance which contained large elliptical nuclei, and broke up into branches. Along with the elliptical nuclei, he found in the protoplasmic substance a number of smaller cells showing all gradations from the large elliptical cells down to the ordinary lymphoid cells of the follicles. The small cells he attributed to a proliferation of the nuclei within the protoplasmic substance, and he figures certain appearances of clusters of nuclei which seemed to point to a process of cell-division. The same protoplasmic condition of the reticulum and the same varieties of cells in its substance are also recorded by Frey in his text-book, and the figure given by the latter (Fig. 389) is entirely confirmatory of the view that is now to be stated of these appearances. Frey mentions incidentally that he had seen the same protoplasmic meshwork in the lymph-sinuses of the mesenteric glands, and that he had seen the fat-molecules of the chyle within the bands of protoplasm; and he adds that he then made the mistake of supposing the reticulum to be "a system of cellular tubes." The true explanation seems to be not that the reticular substance is a fixed system of tubes, but that it can be made tubular by cells passing into it. There is often to be seen, in the course of a fibre, the appearance of a sudden hollow expansion within which lies a nucleus. The out-

lines of the expansion usually taper abruptly, and become continuous again with the narrow fibre beyond; but sometimes the breadth of the fibre beyond the nucleus is hardly less than at the point of expansion. In one of the preparations of the series there was seen a long "fibre" of the lymph-sinus which had no fewer than three separate dilatations on it, each containing a round nucleus, while there seemed to be a free passage in its substance between them. The appearance was not unlike the beaded condition of a double contoured nerve-fibre. Whatever may be the exact process, there is no doubt that the large yellow granular cells become entangled in the meshwork of the lymph-sinus, and thereby lose their pigmented protoplasm. In all probability they travel through a considerable length of sinus, and come in contact with the reticulum many times before they are reduced to their nuclear condition. The disposal of them after this point falls to be considered separately. The use of the lymphatic gland may be compared not so much to that of a charcoal filter, as to that of a winnowing apparatus. In the first step of the process the husk is loosened and detached from the grain or kernel, and in the second step of the process the useful elements are separated and collected together. In addition to those changes, which are effected within the lymph-sinuses, it seems probable that the cells passing through the lymphatic gland suffer further changes in entering the follicular tissue.

In the accounts of the involution and evolution process it was stated that the large yellow granular cells were sometimes reduced to the nuclear condition, with loss of their pigment, while they were still in the mamma. Collections of them can be seen in the fibrillar tissue which show very much the same gradations from the full-sized nucleated granular cell to the naked nucleus, as has been described for those in the lymph-sinus of the lymphatic gland. Again, in the final state of involution, or the resting state, the contracted acini are found to have a few grains of pigment lying free among the resting cells, and in some cases where the free pigment is not seen in the acini it may be seen strewn over the surface of the lobule generally. Now, within the lymphatic gland, the protoplasmic reticulum of the lymph-sinus is not the only agency for reducing the granular cells to their nuclear condition. Fig. 18 is a drawing from the case in which the lymphatic glands

beneath the mamma were in a rudimentary condition; that is, the follicular tissue was at its lowest point, while the lymph-sinuses

FIG 18.

From a lymphatic gland beneath the mamma. The follicular tissue represented by two or three rows of lymphoid cells in the adventitia of a large vein; the lymph-sinus occupied by *large yellow cells* with their substance often drawn out into processes. Magnified 300 diameters.

and the stroma of the hilus were of great extent. The figure shows the section of a large vein, and the follicular tissue is represented by two or three rows of lymphoid cells in its adventitia. Surrounding the vein with lymphoid cells in its adventitia is the large lymph-sinus filled with pigmented cells, many of which are drawn out into processes, as already described, while some of them have their cell-substance reduced in amount. It will be observed that the lymph-sinus is separated from the rows of lymphoid cells by a membrane, which is, as it were, the outermost layer of the loose adventitia of the vein; it appears in the figure as a dark line. This limiting membrane showed in the coloured preparation an interesting condition of things which could not very well be transferred to the figure. It showed at one or two points a pigmented cell as if adhering closely to it, drawn out to a long narrow form, and with its pigmented granules scattered along the membrane for a considerable distance on each side of the cell-mass. The cell was no doubt passing from the lymph-sinus into the follicular area, and losing its pigmented substance in the process. In the preparations of the same case another very definite appearance is often to be seen. In parts

of the gland where the follicles are of considerable size, the surface of the follicle is strewn with numerous grains of pigment approaching to red in colour. These grains are sometimes of considerable size, circular, and with the characteristic dark border. The lymph-sinus surrounding the follicle is full of the ordinary yellow nucleated cells; the pigment of the latter is much paler than that strewn over the follicle. The collections of the darker coloured free pigment are limited exactly to the follicular tissue. The inference seems to be that some of the cells enter the follicles with their pigmented substance, or at least a portion

Fig. 19.

From the medullary part of a lymphatic gland beneath the mamma of a cat: *a*, trabecula crowded with spindle-cells, some of which have the same substance as the large dark cells in the lymph-sinuses (*b*); *c*, portion of a lymphatic cylinder. Magnified 300 diameters.

of it, still adhering, and that the pigment which they lose there is not at once carried away, as it would have been if the denudation had taken place in the sinus through which the lymph-current is passing. There is one other mode of reducing the granular cells

to a nuclear state, which although it may be exceptional, can hardly be passed by without mention. It is represented in Fig. 19, which has been drawn as accurately as possible. The lymphatic glands are those from beneath the mamma in the same case from which Fig. 14 is taken. The latter shows abundant production of the yellow granular cells in the mamma. Now the lymphatic glands did contain traces of yellow pigment, but the large nucleated granular cells that were found in the lymph-sinuses were not often of a yellow colour, but they usually stained very dark by the colouring reagent (logwood). Their granular character is more distinct than in the case of the yellow cells, and they have often a mulberry-like surface. In other respects they are exactly the same as the large yellow cells. They have been found in the mammary lymphatic glands of two other cases somewhat more advanced in evolution, and in the particular case described already, of a lymphatic gland made up almost entirely of lymph-sinuses and pigmented cells in them, they were found here and there among the ordinary yellow cells. There is no doubt that they are only a modification of the large yellow cell as regards its pigment, or in the property of taking on an artificial colour. The portion of gland drawn in the figure is taken from medulla not very far from the hilus. Portions of three cylinders of the medulla occupy the outer parts; next to them come the corresponding lymph-sinuses, and in the centre running horizontally, is a broad trabecula with an extension upwards. The lymph-sinuses show indistinctly the fibres of the reticulum, and they contain, besides a number of the large granular cells, many nuclear cells of various sizes. If the trabeculæ are examined, they are found to present a very singular appearance. They are crowded with staff-shaped or spindle-shaped cells (or nuclei), which follow the direction of the trabecular fibrils with their long axis. About one-fourth of the elongated bodies have the intensely dark granular appearance of the large round cells in the sinus, and these are also the largest and broadest; the majority of the elongated elements are narrower, pale and granular, and there are transition stages as regards depth of staining and shape between those two kinds. The contention is that the elongated cells in the trabecula have penetrated from the lymph-sinus, and have acquired their shape in passing through the narrow interfascicular spaces. No other explanation of this picture,

as a whole, suggests itself. The staff-shaped nuclei, if not the spindle-shaped, have often been seen in the trabeculæ of lymphatic glands, though they do not appear to have been figured before in such numbers or in such variety. The usual account of them is that they are the nuclei of involuntary muscular fibres; but it has been pointed out already that some authorities are not satisfied with the histological evidence for this allegation, and that W. Müller, in weighing the evidence, is led to accept the theory chiefly because the lymphatic glands have been shown to contract under an electrical stimulus.

The presence of plain muscular fibres in the trabecular and capsular tissue of lymphatic glands is a matter that does not in any way concern the general purpose of this investigation; and if those fibres have actually been isolated by means of dilute nitric acid in "highly characteristic" forms, it is futile to offer any other exclusive or dogmatic explanation of the appearances in the trabeculæ as they are seen in sections. At the same time I do not doubt that Fig. 19 represents a crowd of circulating cells passing through the substance of the trabeculæ, instead of or in addition to passing through the meshwork of the sinus. The difference between the trabecula and the meshwork of the sinus is not so very great as it appears at first sight. The "fibres" or protoplasmic bands crossing the sinus are simply bundles detached from the side of the trabecula; the reticulum of the lymph-sinus is a frayed-out condition of the trabecular tissue. By following the edge of a trabecula it is easy to see "fibres" detaching themselves from it, or to trace the continuity between fibres of the sinus and the outermost bundles of the trabecula. The fibre usually crosses the sinus from the trabecula in such a way as to make a small angle with the latter, and a circulating cell of the lymph that had been driven into that angle would, in its further progress, necessarily enter the substance of the trabecula. There are appearances in the preparation from which Fig. 19 is taken that seem to bear out that notion. Again it is not to be forgotten that the cells or nuclei in the trabeculæ vary very much in different cases, not only in number but also in shape—many of them being round—and that circumstance is hardly consistent with the theory that they are all the nuclei of plain muscular fibres.

The correctness or incorrectness of the explanation given of

the staff-shaped and spindle-shaped cells in the trabeculæ in Fig. 19 has a bearing on the question already raised with reference to Fig. 16. The latter is held to show a particular form of the waste products of evolution on their way through the interfascicular spaces of the mammary interlobular tissue, and the exactly analogous occurrence in the trabecular tissue of the lymphatic gland may be held to give an independent support to that view.

Up to this point we have found one function at least of the mammary lymphatic glands to be the reduction of the granular waste-cells of the secretion to the status of nuclei. We have seen that such denudation takes place chiefly among the protoplasmic fibres and bands stretched across the lymph-sinuses, but that a similar change is effected on the large waste-cells in their passage through the limiting membrane of the follicles or cylinders, or in their passage through the interfascicular spaces of the trabeculæ. The special use or significance of the follicular tissue of the gland has not yet been touched upon, and although that is a more difficult point than the preceding, some of the preparations of this series are not without instruction as to it. The Fig. 20 is taken from a case already referred to. The lymphatic glands were quite small bodies in the midst of the cushion of fat beneath the mamma in the inguinal region. They seemed to the naked eye to be composed almost entirely of yellowish pigmented material, which was found to be the waste material of the secretion; and it appeared as if the conveyance of so large a quantity of waste-cells to a particular point in the fat-tissue beneath the mamma had given occasion for a lymphatic gland to develope itself, its framework being derived from certain fixed elements of the part—blood-vessels and stroma—and its parenchyma being formed by the waste material in its crude or in its subsequent transformed state. Without raising the question, whether a set of lymphatic glands may not have at one time existed at that part of the fat-tissue only as an empty framework, it does appear from the examination of the glands as they were found, that their chief and earliest constituents were the dense and abundant stroma of the hilus, the large lymph-spaces, and the blood-vessels. The glands were in fact rudimentary glands, and that not in the sense of embryonic development, but in the sense of a disused function being suddenly

revived. The animal was aged; and the great production of waste-cells, though it followed in the track of the evolution of

Fig. 20.

From a lymphatic gland (same case as Fig. 18). In the centre of the figure is the longitudinal section of a vein which discharges below into a larger vein; the follicular tissue is represented by rows of lymphoid cells in the adventitia of the vein, and especially of its branches; the lymph-sinuses are filled by *large yellow granular cells*. Magnified 150 diameters.

the breast, was not due to the ordinary cause of evolution, but to some unknown pathological excitation. If the drawing be

referred to, it will be seen that the dense fibrillar stroma of the hilus is the most abundant tissue; that it is penetrated in various directions by wide lymphatic spaces, the lymph-sinuses; and that the follicular tissue is represented only by a few rows of lymphoid cells in the walls of the veins. One of the latter is shown in longitudinal section, with several branches. Beginning at the top of the figure, there is seen at the left-hand corner a considerable follicle or cylinder, in the centre of which is a vein. On the other side at a corresponding point, there is another cross section of a vein with a smaller number of lymphoid cells round it, and if the longitudinal vein be traced downwards, it will be seen that the lymphoid cells which form two or three rows at its upper part and round its branches, diminish in number at its lower part, and, where the vein opens into the large venous trunk at the bottom of the figure, that they are altogether wanting. The figure is nothing less than a diagram of the plan of a lymphatic gland on a small scale. The blood-vessels have long been known to run in the axis of the lymphatic cylinders, and several writers[1] have suggested what is undoubtedly the true account of the relation of the lymphoid corpuscles to them. They have described the cylinders of the gland to be simply the loose adventitia of the blood-vessels containing lymphoid cells. This view of the matter at once places the follicular tissue of the lymphatic glands in the same category as the follicular tissue of the spleen. The Malpighian bodies seated on the fine arterial twigs are to be considered as true lymph-follicles; they form circumscribed thickenings on the walls of the arteries, and are to be viewed as simple deposits of colourless cells (lymph-cells) in the interspaces of the adventitia. In many animals the alveolar thickenings are not circumscribed, but are more uniformly distributed over the arterial wall. It is to be noted that in the spleen the collection of lymphoid cells takes place in the walls of the arteries, and that in the accounts of lymphatic glands, the arteries and veins are not spoken of separately, but the blood-vessels in general. In all the preparations of the above case it appeared to be the adventitia of the veins in which the lymphoid cells were collected. Such, then, appears to be

[1] Leydig, *loc. cit.*; Billroth, *Beiträge zur pathol. Histologie*, Berlin, 1858.

the relation of the trunks of the vessels to the lymphoid cells in the centre or hilus of the gland; the cylinders of the medulla are essentially their loose adventitia filled with lymphoid cells. When we come to consider the follicles of the cortex, a corresponding explanation of them may be given. The medullary cylinders contain all the larger blood-vessels, which are provided with stout adventitia; some of their branches break up into capillaries on the cylinders, and the rest proceed to the cortex of the gland. As the vessels divide into smaller branches, the looser does the connective tissue of the adventitia become, and at length there appear, in the place of connective-tissue fibres, "cytoblasts" whose cell-membranes enclose narrow spaces, and which are provided with two or three thread-like processes[1]. It is in that reticulum that the lymphoid cells lie, generally two or three of them in one mesh. The small-meshed reticulum of the follicles is simply a modification of the adventitia of the terminal vessels. At the same time we have seen in these preparations (Fig. 20) that the smaller the vein is, the larger is the collection of lymphoid cells in its wall. As the cortex or periphery of the gland is approached, one finds that the adventitia of the vessels is frayed out into a spacious meshwork, and that the lymphoid cells have proportionately increased in number.

Some facts have been mentioned already to show that the waste-cells are sometimes denuded of their substance and pigment in passing from the lymph-sinus into the wall of the vein, *i.e.* into the follicular tissue; and it is probable that the cells that have been reduced to the nuclear condition in the lymph-sinus itself, or in the substance of the trabeculæ, enter the cylinders and follicles in the same way. This brings us to consider what is the further effect of the lymphatic gland on the waste-cells brought to it, besides the two uses of it which have been compared to the uses of a winnowing apparatus. The lymphatic follicles no doubt represent the heaps of cells that have been cleared of their pigmented and granular cell-substance; the follicles are a sort of reservoir in which they collect, and from which they may be again swept out into the lymph-current, in the manner described by His in a passage already quoted. But

[1] Brücke, *Ueber die Chylusgefässe und die Resorption des Chylus*, p. 34, 35.

they have evidently another purpose. The meshwork of the follicle differs considerably from that of the lymph-sinus; the meshes are very much finer, and they are of a uniform size. If the lymph-sinus in Fig. 19 be examined closely, it will be seen to contain some very large nuclei, and some of the ordinary lymphoid size; the large nuclei have a distinct linear contour, a pale homogeneous substance, and a comparatively large nucleolus. Their origin in this particular case belongs to a former part of the inquiry; they are probably the characteristic waste products of the middle period of evolution. It may be said of lymphatic glands in general that the cells in the lymph-sinus are not only fewer than those in the follicles and cylinders, but that they are also a size larger and that their substance is paler. There appears to be sufficient evidence, more especially in the remarkable case from which Fig. 18 and Fig. 20 have been taken, that cells do leave the lymph-sinuses and enter the follicular tissue. In so doing, they would pass from a network of large and irregular meshes to a network of smaller meshes of a uniform size. Those differences in the reticular tissue of the two situations correspond to differences in the cells that respectively occupy them; the cells of the lymph-sinus are of various sizes and on the whole large, while those of the follicular tissue are of a uniform smaller size. The conclusion seems justified in the case of the cells brought to the lymphatic glands from the breast, that as the network of the lymph-sinuses strips some of them of their pigmented cell-substance, so the follicular meshwork may reduce others of them to the uniform size of lymphoid cells.

We have thus followed, step by step, the evidence to show that the waste-cells of the mamma enter the special lymphatic glands of the organ, that they undergo various degrees of change according to their requirements, and that they do not leave the gland till they have acquired a uniform size. The finishing touch of their reduction takes place in the follicles, and from these they issue on a new career. All that has been asserted of the follicles as matricular organs for the formation of lymphoid cells may be asserted of them, *mutatis mutandis,* as organs for the final moulding of the same.

The utilisation of the waste products of the mammary secre-

tion naturally implies a large addition, present or future, to the number of white corpuscles in the blood; and such an increase is found to take place during pregnancy. This subject attracted the attention of Virchow at an early period and is discussed in his *Gesammelte Abhandlungen.* In the *Cellular-Pathologie* he describes it as a case of physiological leucocytosis. In his earliest notice he pointed out that those periodical changes of the blood did not take place within the blood itself; the cause of them lay without, and he specially mentions "organs of secretion and reception, but especially the proper matricular organs of the blood, among which the lymphatic glands must be placed first[1]." In the *Cellular-Pathologie* the subject is noticed as follows: "In proportion as a pregnancy advances, as the lymphatic vessels of the uterus enlarge, as the *Stoffwechsel* in the womb increases with the development of the fœtus, the lymphatic glands of the inguinal and lumbar regions become considerably enlarged, and sometimes to such an extent that if we found them at any other time we should say they were inflamed. This enlargement brings to the blood more and more new particles of a cellular nature, and so the number of colourless corpuscles rises from month to month[2]." The pelvic region must no doubt be held to be the chief source of the physiological leucocytosis of pregnancy, but there is every reason to believe that the abundant cellular waste products of the breast contribute also to that condition. As to the fact of a leucocytosis in the animals used in the study of the evolution of the mamma, the observations were not conclusive. The point was neglected in the earlier cases, and in only two of the later was the increase of white corpuscles very marked. In both of these there were from 30 to 50 in the field of the microscope[3].

[1] *Loc. cit.* p. 760. [2] *Cellular-Pathologie*, p. 229.

[3] There is another class of appearances in pregnancy, besides the leucocytosis, on which the study of the evolution of the mamma throws some light. These are the peculiar deposits of pigment. Those of them that occur in women along the lower part of the linea alba, are perhaps to be referred to a corresponding local source in the pelvis. The pigmentation of the areola may be referred directly to the pigment production within the mamma during evolution. It is obvious that if the pigmented cells in Fig. 13 travelled along the submucosa of the ducts all the way to their orifice, instead of breaking into the lumen, they would form a deposit of pigment in the areola; and that may reasonably be supposed to be the track along which the pigment is carried, even if there is no actual transport of the original pigmented cells.

CHAPTER IV.

THE DEVELOPMENT OF THE BREAST.

THE opinion that is at present generally accepted on the development of the breast is that it is a complex extension downwards of the ectoderm. From observations made on the human fœtus, it is said to begin, in the fifth month of fœtal life, as a solid rounded process of the *rete mucosum;* before the seventh month, this wart-like body has thrown out a number of offshoots from various points of its circumference. From that rudiment the whole complex structure of the gland is said to grow out by a process of continuous extension. The rudiment of the gland is at first solid, and the excavation of cavities throughout the various extensions of the rudiment is associated with the formation of fat-containing cells in their interior. These fat-containing cells, by means of which the channels of the gland are formed, constitute the milk of the new-born, which is therefore a developmental product[1].

The development of the breast is thus held to be a process of budding from the mucous layer of the skin, and the homology of the organ is always sought for in other accessory cutaneous glands, and chiefly in the sebaceous glands. The acquisition of the mamma as a mammalian characteristic has also been discussed by distinguished writers in a speculative way from the same point of view; it has been supposed that external agencies acting upon the skin-glands of a particular region have modified them in such a way as to form the milk-gland.

[1] Kölliker, *Entwicklungsgeschichte*, 1st Edition, p. 345.

It will appear, however, on inquiring into its source, that the notion of the mamma being a continuous extension downwards of the skin, and the important doctrine of homology that is based thereon, are supported by evidence of a fragmentary and more or less casual kind, which was probably never intended to be accepted as final. The first statements on the development of the breast appear to have been made by Kölliker in an early edition of his *Gewebelehre*, and are substantially the same as those already quoted from his *Entwicklungsgeschichte*. Every one who is familiar with the text-books of that author will recognise the great services that he has rendered to histology and development by filling up from his own observations many of the blanks that a systematic writer on those subjects is apt to encounter; and his account of the development of the breast must be judged as one of those occasional and sometimes incomplete descriptions. It has, however, had the fate to determine the character of all subsequent opinion on that subject down to the present time. Within a short time of Kölliker's first reference to the subject, a memoir was published by Langer on the human breast, which included an account of the development. The conclusion of Langer is, that "the first development of the mammary gland is bound up with the existence of a peculiar and independent body (*an die Existenz eines eigenthümlichen, selbständigen Körpers gebunden*), in which the ducts develope without connexion with the groove in the skin; the ducts are therefore not invaginations or processes of the outer skin (*somit keine Ausstülpungen oder Fortsetzungen der äussern Haut sind*[1].") It appears to me that that conclusion differs from the view of Kölliker in essential points; but in the work of Remak, which holds a position of authority in the literature of development, the two authors, Kölliker and Langer, are curiously enough quoted together and without distinction as having shown that "the mammary glands, like the sweat glands, are formed from the Malpighian layer of the upper skin[2]." There has thus arisen an apparent unanimity as to the development of the mamma by ingrowths from the ectoderm, and that view still passes unquestioned.

The plan according to which most of the secreting glands of

[1] *Denkschriften der Wiener Akademie*, 1852.

[2] *Untersuch. über die Entwickl. der Wirbelthiere*, p. 100.

the body, including the breast, are supposed to develope, is that the rudiment commences as a downward process of the epithelial surface on which the gland, in its mature state, will pour its secretion. The gland is essentially a very complex reduplication of the epithelial surface[1]. The development of the gland, according to this view, may also be said to be centrifugal; the growth takes place by the throwing out of processes from a central point of the surface towards a wide periphery at the depth. The botanical terms of "bud," "offshoot," &c., are constantly used to describe the process of formation of a racemose gland. The structural growth, however complex, is held to be one of continuous extension downwards, just as the growth of a plant is an extension upwards. The ducts of a gland grow like the branches, and the acini unfold like the leaves. But it must be held at the outset to be an abuse of terms to transfer, in so facile a manner, the language of plant-growth to the formation of a racemose organ within the body. It is only under exceptional circumstances, as for instance in watching the formation of blood-vessels in the tadpole's tail, that one can observe the actual process of extension; and there is reason to think that writers on development have not always respected the difference between the facts derived from immediate observation and the facts derived from mediate evidence. In the microscopic examination of dead tissues one never observes anything but co-existences, but in descriptions we use the language of succession; and, even if no fallacies have crept in through such laxity of expression, the evidence that is needed to make the mediate truth of the same value as the truth of direct observation is apt to be deficient. The conclusions that I shall endeavour to make good in this chapter are radically opposed to the current view of gland-development. If the development of glands, as generally accepted, be called a centrifugal process, the process that I shall describe for the breast may be called centripetal; the secreting structure is formed in a layer (of mesoblast) beneath the outer skin, and the ducts or communications with the skin are essentially secondary formations owing their existence to a force from within. The same

[1] "The plan of augmenting the secreting surface by *recession* or *inversion* of the membrane, in form of a cavity, is, with few exceptions, that generally adopted in the construction of secreting glands." Quain's *Anatomy*, 8th Ed. Vol. II., p. 234.

principle may or may not extend to other secreting glands [1]; the breast is at least one of the most favourable cases in which to exemplify it, from the circumstance that it developes late in fœtal life and in a region where the surface-cells are at that period easily distinguished from the deeper tissues.

Although the doctrine of continuous extension from a central point on the surface has been practically the only one hitherto admitted, an entirely different account of gland-development had been put forward in 1842 by Goodsir. Those remarkable and far-reaching views of Goodsir can hardly be said to have gained currency, perhaps owing to the aphoristic manner in which they were expressed. They are for the most part stated in naked propositions, without the support of the laborious details on which they had no doubt been based. Goodsir's statements are as follows [2]:

[1] A somewhat similar view, with an important reservation as to the ducts, has lately been put forward by Schenk for certain other glands. In an investigation on the development of the pancreas, he draws a distinction between the source of the secreting cells of the organ, and the epithelial lining of the ducts. He derives the former from the mesoblast, and the latter from the hypoblast (Die Bauchspeicheldrüse des Embryos, *Anat. u. Physiol. Untersuch.*, quoted in Foster and Balfour's *Embryology*, p. 133). In his *Lehrbuch der Vergleichenden Embryologie der Wirbelthiere*, the same author states this opinion more generally. Speaking of the development of glands connected with the epithelial-glandular layer he says: "Wir müssen hier gleich anfangs darauf aufmerksam machen, dass man die Anlage der sogenannten Darmdrüsen, deren Entwicklung nach Remak im innern Keimblatte stattfindet, nicht im Sinne der älteren Autoren auffassen kann, dem zufolge die einzelnen Anhangsorgane des embryonalen Darmes, wie Lunge, Leber, &c., Ausstülpungen des Darmkanals wären. Vielmehr sieht man sich genöthigt, an diesen sämmtlichen Organen nur insoferne das Darmdrüsenblatt als betheiligt anzusehen, als diess bloss Epithelialgebilde, für die Auskleidung der einzelnen Ausführungsgänge oder deren Verzweigungen abgiebt. Die Elemente, welche das Parenchym dieser Organe ausmachen, werden zumeist der Urwirbelmasse entnommen, welche den Darmkanal umgiebt," pp. 88—90. Although Professor Schenk here speaks of the doctrine to which I have referred in the text as being the view taken by "the older authors," it is still supported by writers who are decidedly modern. Professor Boll has lately published a pamphlet (*Das Princip des Wachsthums*, Berlin, 1876) which aspires to supply the long-delayed reason why, in the development of glands, the mucous membrane grows inwards as Remak described. The formation of the gland, he concludes, is not the result simply of the epithelial membrane growing inwards, but it is the issue of a conflict between the epithelial membrane growing inwards and the blood-vessels growing outwards.

[2] *Anatom. and Path. Observations*, 1845, p. 32; or *Anat. Memoirs*, Vol. II. p. 425.

"The blastema, which announces the approaching formation of a gland in the embryo, in some instances precedes, and is in other instances contemporaneous with, the conical blind protrusion of the membrane upon the surface of which the future gland is to pour its secretion.

"In certain instances it has been observed that the smaller branches of the duct are not formed by continued protrusion of the original blind sac, but are hollowed out independently in the substance of the blastema, and subsequently communicate with the ducts.

"It appears to be highly probable, therefore, that a gland is originally a mass of nucleated cells, the progeny of one or more parent cells; that the membrane in connexion with the embryo gland may or may not, according to the case, send a portion of the membrane, in the form of a hollow cone, into the mass; but whether this happens or not, the extremities of the ducts are formed as closed vesicles, and then nucleated cells are formed within them, and are the parents of the epithelium cells of the perfect organ."

These summary statements are prefaced by the remark:

"We require renewed observations on the original development of glands in the embryo. From the information we possess, however, it appears that the process is identical in its nature with the growth of a gland during its state of functional activity."

It is the latter subject that chiefly engaged Goodsir's attention. His observations were made on animals in which the glands have particular periods of functional activity. The sexual glands of certain vertebrates as well as invertebrates were studied during those periodical processes of "development, maturity and atrophy," which they undergo from season to season; and it is with the periodical processes that he says the embryonic development is identical. The great significance of that remark will be discussed in the next chapter; but a short extract will be useful at present to illustrate further Goodsir's view of the embryonic development of acini. The above-quoted statement that "the extremities of the ducts are formed as closed vesicles" will become clearer from the following, relating to the periodical "development:"

"An acinus is at first a single nucleated cell. From the nucleus of this cell others are produced. From these again, others

arise in the same manner. The parent cell, however, does not dissolve away, but remains as a covering to the whole mass, and is appended to the extremity of the duct. Its cavity, therefore, as a consequence of its mode of development, has no communication with the duct.

"The original parent cell now begins to dissolve away, or to burst into the duct at a period when its contents have attained their full maturity. This period varies in different glands, according to a law or laws peculiar to each of them.

"In the gland, there are a number of points from which acini are developed, as from so many centres. These I name the germinal spots of the gland."

The following account of the development of the mamma in the guinea-pig will be found to support Goodsir's general view of gland-development[1].

In the new-born guinea-pig the mamma is found in the inguinal region on each side, extending obliquely downwards and backwards from the single nipple. If a vertical section be made in a line running from the nipple inwards toward the symphysis pubis, the tract of mammary tissue will be exposed. In a preparation hardened in alcohol it appears as a somewhat narrow strip of whitish tissue about half an inch in length and running through the midst of a large body of fat-tissue. From the long central tract, short offshoots project into the surrounding fat.

In embryos about two-thirds grown, the mammary rudiment is found to have the same relative position and extent. In the section of the prepared tissue there is not the same naked-eye distinction between the tract of mammary tissue and the surrounding fat. Mamma and fat together form a small pear-shaped body beneath the skin, the pointed end terminating anteriorly at the nipple.

At both of the stages here mentioned, the developing mamma is found to have relatively its full dimensions, and to lie amidst a

[1] The similarity of methods and conclusions with those of Goodsir, both in this and former chapters, is quite undesigned, for I had published the investigations on the periodical processes of the breast and a preliminary notice of its development, before I became acquainted with his memoir on "Secreting Structures." That paper does not specially refer to the breast, but its general conclusions agree closely with those that I arrive at in the particular case.

quantity of fat-tissue; the plan of the organ is, as it were, laid down over its whole extent. In the earlier of the two stages, the acini have not begun to appear distinctly, but only the system of ducts. At the time of birth, however, the acini are found in active development, and within a few days after birth they are sometimes found to have so great an expansion as to completely overshadow the system of ducts.

The development of the system of ducts can be best considered after that of the acini has been described, for reasons that will appear. The contention of the first part of this chapter is that the acini, or essential secreting structure of the breast, develope from a matrix-tissue at numerous scattered points or centres ("germinal spots" of Goodsir); that the matrix-tissue or embryonic cells are the same from which the fat surrounding the mamma developes; and that the mode of development of the acini is, for the individual cell, exactly the same process as in the development of the fat-lobules. The mammary gland would therefore be a further specialisation of fat-tissue, and a product of the mesoblast. It has been said that the opinion of the mamma being a complex extension of the ectoderm has gained currency somewhat too easily, and that a sufficient proof of this process of continuous extension from the skin would be really an arduous matter. But if it is difficult to prove that origin of the mamma by direct evidence, it is no less difficult directly to disprove it. To make out a parallelism, however, between the development of the mammary acini and the development of the adjacent lobules of fat is perfectly fresh ground; and that parallelism, and the identity of the matrix in the two cases, will be the issue raised.

The resemblance between the mode of origin of the fat-lobules and of the mammary acini is first suggested by that stage of the development of the breast which is represented in Fig. 1 (of the plate). The figure represents a mammary lobule in a guinea-pig four days old. The expansion of the lobule is very considerable, so much so that the branches of the duct are completely obscured by the acini. Each acinus is a rounded space distended by large vacuolated cells like fat-cells, among which a number of nuclei lie at various depths. If reference be now made to Fig. 2, which shows the condition of the breast in a guinea-pig that was estimated from its size to be about two or three weeks earlier, some idea

will be obtained of the way in which this great expansion of secretory structure comes about. In the earlier of the two stages of development, there are present only the ducts, representing the framework of the gland, and around them a quantity of embryonic tissue. It is from this field of embryonic tissue that the cluster of acini, as shown in Fig. 1, have sprung up. Now, at the earlier stage of development shown in Fig. 2, a development of the matrix-cells into fat-cells has already taken place at various points; the space immediately surrounding the rudimentary lobule in the figure is occupied by fat-tissue, although the drawing has not been extended so far. It will thus appear, that if the mammary acini and the fat-lobules that surround them develope from the same matrix, the fat-development is considerably in advance of the development of the secreting structures. The contention is that the embryonic tissue nearest to the already formed ducts is left to undergo a later and somewhat more special differentiation.

It might therefore be supposed that the mammary region of the guinea-pig contained within itself, at various periods of embryonic life, all the elements for a comparison between the development of collections of fat-cells and the development of acini. The assertion is that from one and the same matrix there develope first a certain number of fat-lobules, and afterwards the acini. The peculiar cellular transformation that leads to the production of fat-lobules in certain parts of the matrix is the same that, two or three weeks later, leads to the formation of acini in the surviving or untransformed part of the matrix. But that apparently simple question cannot be put to a satisfactory proof in the guinea-pig alone. It so happens that the parallelism between the fat-development and the development of acini can be much more clearly traced by studying the course of fat-development in the inguinal region of the fœtal kitten; and the reason of this will now be explained by a statement of the anatomical characters of the mamma in the two animals.

In the adult guinea-pig the mamma on each side is a flattened pyramidal body, the apex of which is at the nipple and the base towards the groin; its length is nearly two inches. The mammary structure proper is of a reddish-brown colour, and is surrounded on all sides by a large quantity of fat. In a vertical section of the entire organ, including the fat, the brownish parenchyma of the

gland appears as a central wedge, sending out processes into and interlocking with the fat on all sides. The mamma is not separable from the fat without dissection, but the mamma and fat together form a flattened pyramidal mass which is loosely connected with the surrounding tissues. On the other hand, the mamma of the cat on each side is an extensive broad and flattened strip of glandular substance extending from the groin to the upper part of the thorax, and supplied with four or five teats at intervals corresponding to the systems of ducts of four or five originally separate glands. It is only at the inguinal end that there is a considerable quantity of fat; it there forms a thick cushion beneath the gland. The mamma is an expanded layer or stratum of purely glandular structure, which rests, chiefly at its inguinal end, upon a cushion of fat. Whereas in the guinea-pig the fat could be separated from the gland only by a thorough dissection, in the cat it could be at once removed in a separate layer.

Corresponding to those anatomical differences in the adult condition of the two animals, there are remarkable differences in the development. What may be called the mammary fat developes in the kitten not only in the plane beneath the mamma, but it developes as an independent *organ.* This organ is a *fat-body,* not differing, except in its ulterior development, from the fat-bodies that occur in other classes of animals in various situations and endowed with various functions. But there is another important difference between the mammary fat of the kitten and that of the guinea-pig. In the fœtal guinea-pig the fat has passed through its embryonic transformation and has reached its nearly perfect or mature form two or three weeks before birth. In the kitten the fat, developing as a fat-body, is still undergoing its developmental changes up to, and in some cases a few days beyond, the time of birth. The development of the mammary fat is a very much tardier or more gradual process in the kitten than in the guinea-pig. From this circumstance, and from the circumstance of its development as a separate organ or fat-body, or rather from both circumstances combined, the comparison can be best made between the mammary fat of the kitten, on the one hand, and the acini of the guinea-pig on the other. An interval of two or three weeks occurs in the guinea-pig between the fat-development and the formation of the acini, and the same interval of time occurs between

the completion of the fat-development in the guinea-pig and that in the kitten; so that, although the mammary acini in the new-born guinea-pig are comparable to its fat-lobules two or three weeks before birth, they are also comparable to the fat-lobules of the kitten of its own age; and that comparison is much the more striking of the two. There is reason to think that the development of the mammary acini in the kitten follows that of the fat-lobules at a short interval, as in the guinea-pig, and that it takes place on the upper surface, or adjoining the youngest part of the fat-body; but the development of the acini will be explained for the guinea-pig only. The kitten will therefore be used to explain the fat-development in the inguinal region, and the guinea-pig to explain the mammary development; and it will be most convenient, in order to make a comparison between the two processes, to commence with an account of the former.

The description now to be given of the development of the fat-tissue in the inguinal region of the kitten, or, in other words, of the inguinal fat-body of the kitten, does not differ essentially from that given by Toldt[1]. The chief points of immediate interest stated by that author are as follows. In the earlier months of embryonic life the fat-cell is a round and finely granular cell with a nucleus, but without a cell-wall, and differing from a colourless blood-corpuscle only in point of size; at this stage the fat-cell is already differentiated from a connective-tissue cell. The development of the fat-tissue is always directly bound up with the existence of a system of blood-vessels; if three or four cells are found grouped together as the rudiment of a fat-lobule, this grouping is already in connexion with blood-vessels. By reason of the characteristic and independent system of blood-vessels for the fat-tissue, there is suggested a close analogy between the aggregate of fat-lobules and an acinous gland[2]. Those aggregates of fat-lobules are the fat-bodies. It is in the form of independent organs that the future fat-tissue occurs in the embryo stage of some mammalians, while these bodies persist through life in batrachians. In insects, they are organs of great importance, and of various functions. The fat-

[1] *Sitzungsberichte der Wiener Akademie*, 1870, p. 451.

[2] Professor Toldt's words are: "There can be no more perfect analogy than that which subsists between the fat-tissue and the so-called acinous glands, in respect of the distribution of their blood-vessels."

body in the inguinal region of the new-born kitten is one of those described by Toldt; one of the figures in illustration of his paper gives an excellent idea of the perfect and independent vascular supply of the fat-body.

The pair of fat-bodies in the inguinal region of the new-born kitten are at first sight exactly like a pair of secreting glands. They are about half an inch in length, somewhat curved, and placed back to back; their posterior end is thick and rounded, and anteriorly they become narrower and pointed. Their anterior ends, at the time of birth, correspond almost exactly to the inguinal pair of teats of the kitten. The blood-vessels may be seen ramifying on their lower and flattened surface, a large trunk running exactly in the centre from behind forwards, and giving off branches symmetrically on each side. The bodies have a loose fibrous investment, which isolates them throughout most of their extent; but at the upper and anterior end they cannot be detached without some tearing of their substance. In other words, their anterior extremity is not definitely rounded and circumscribed as the posterior is. They have the parenchymatous consistence and pinkish colour of a secreting gland, when fresh; after hardening in spirit, they become more spongy. Microscopic sections of them present a characteristic appearance. The lobules are large at the posterior end of the body; the smallest groups of cells are met with at the upper and anterior end. Each lobule is a closely packed mass of large cells with very striking characters (Fig. 3, C). The substance of the cells is a granular protoplasm, and in all of them it is occupied by one or more vacuoles. Generally there is only one large vacuole occupying the lower segment of the sphere, while the protoplasm is chiefly massed at the other pole of the cell, and appears in section as a crescentic band. The nucleus has usually an excentric position in the midst of the crescent-shaped band of cell-substance. The boundary of the cell, or the wall of the vacuole, is also formed by the same granular substance, forming a narrow belt or ring at the opposite pole. These cells have all the character of secreting cells; if there were an outlet for their fluid contents, the fat-body might be viewed as a gland. But a few days after birth, this developmental appearance passes away; the cells of the fat-body are so completely excavated and filled with fluid that their granular substance disappears, and the

original protoplasmic cell is represented only by a thin sac-like membrane filled with an oily fluid. Instead of the vacuolated cell giving up its fluid contents, as in a secretory process, it retains the fluid permanently. At the same time the individual cells expand greatly, and the fat-body becomes a mass of fat which extends forwards and laterally.

Many of the cells found within the developing acini of the mamma (in the guinea-pig) have the closest resemblance to the vacuolated protoplasmic cells of the fat-body (in the kitten), and this resemblance is so striking, that the young fat-lobules might be mistaken for portions of the actual gland. There is, however, no identity between the fat-body, or any part of it, and the mammary secreting structure; but there is an identity in the matrix-tissue of both, and a remarkable parallelism in their respective developments. This parallelism will now be explained, first by tracing the fat-body (of the kitten) backwards to its origin, and afterwards by describing the mode of origin of the mammary acini (in the guinea-pig).

The various representative stages of the fat-body are shown in A., B, and C of Fig. 3, that shown in C being the stage just described above as immediately preceding the final or mature condition of the fat-tissue. The condition in B, taken from an embryo kitten about 3½ inches long, or about two-thirds grown, is the characteristic earlier stage; while A, from an embryo kitten 2½ inches long, shows the earliest collection of cells that can be identified as going to form a fat-lobule. The fat-body, which, at the acme of its development, is an isolated parenchymatous organ with a separate vascular supply, commences at many scattered points in the inguinal region. The small groups of cells that afterwards become fat-lobules first show themselves at the extreme inguinal end of the abdominal wall. Between the abdominal muscles on the lower side and the *rete mucosum* on the upper, a wedge-shaped mass of gelatinous tissue occurs, the pointed end being forwards. It is in this subcutaneous matrix that the clusters of fat-cells take origin. The appearance of the matrix-tissue is shown in Fig. 3, A. Spindle-cells occur somewhat sparsely in the midst of a ground-substance which is hyaline when fresh, but assumes a granular or thready appearance after coagulation by reagents. At an earlier period, the embryonic cells of this region are relatively much more nu-

merous. The spindle-cells are the ordinary embryonic cells of the mesoblast, persisting to a comparatively late period of fœtal life. At a number of points, such as the one shown in the centre of the figure, cells are massed more closely. There is no reason to suppose that these groups of cells are derived from any other source than the spindle-cells of the part. The group begins to form by the subdivision of one of the embryonic cells; the progeny are more globular, and with a larger amount of protoplasm round the nucleus. The differentiation towards a fat-lobule has already begun, and the divergence from the spindle-cell or cell of the connective-tissue type goes on increasing. The small clusters of spherical protoplasmic cells expand; the cells at the same time become larger and more like epithelium, the growing lobule having the appearance shown in Fig. 3, B. In the oldest part of the fat-region, the lobules are already large and packed closely together; although the fat-body is not yet encapsuled or isolable as a whole, yet the space between the skin and the abdominal muscles is readily seen to be occupied by a special kind of tissue, forming a wedge-shaped mass which, in alcohol preparations, has a whitish appearance. The largest lobules are many times the size of the section figured, and their cells, representing a passing phase in the development, often have a close resemblance to cubical or polyhedric epithelial cells. About the time of birth the fat-body has acquired the appearance of being an independent organ, and the cells are all vacuolated as in Fig. 3, C. During the development of the fat-body, one or more lymphatic glands have developed towards its lower surface and as if enclosed by it.

Throughout the growth of this body or organ, the development, as has been already stated, is not in an equally forward state at all points. The groups of fat-cells first appear at the extreme inguinal end of the region, and the order of appearance of the various centres of development is, throughout the whole process, from behind forwards and from the deeper parts towards the surface. Again, when the fat-bodies are already of considerable size in the groin, the corresponding formation of fat-tissue at separate points, beneath the three or four anterior pairs of teats in the kitten, has not advanced beyond the first stage of small scattered groups of embryonic cells. In these anterior regions of the abdominal and thoracic walls, the fat is at no period of its existence found as a

separate body or organ, although the early stages of its formation are the same as in the actual fat-body of the groin. Limiting the attention again to the latter, the first steps of development may be observed at its anterior end, and on its upper surface, and even in the tracts of embryonic tissue that lie between the lobules, at a time when the development as a whole is well advanced. It is beside those tardier points, at the anterior end and on the upper surface, that the first appearance of mammary secreting structure must be looked for. In the cat I have not succeeded and indeed have hardly attempted to trace the formation of the mammary acini from the embryonic tissue of the upper surface of the fat-body. If it be necessary to carry out the alleged parallelism in the same animal, it must suffice to state the hypothesis that in the cat the mammary acini begin where the fat ends, and that the latest differentiation of the embryonic cells in the fat-region is appropriated to a still more particular purpose, that is, to become the secreting structure of a gland. But at this point the field of observation must be changed from the cat to the guinea-pig.

It has been already explained that, whereas in the cat the lower end of the mammary gland lies altogether above the fat-body, or rather above the cushion of fat into which the latter is changed; in the guinea-pig, on the other hand, the mamma and the fat-tissue are interlocked on all sides, and the mamma is limited to the inguinal region. Whatever these differences may signify, the guinea-pig is on account of that characteristic a more convenient animal on which to demonstrate the present theory of mammary development. The fat-lobules of the mammary region in the guinea-pig do not form a fat-body; they never pass through the remarkable gland-like phase that the fat-body of the kitten is so well adapted to illustrate. But, on the other hand, the mammary development takes place in the midst of the fat-development, and it is therefore easier to show that the matrix-tissue of the two kinds of structure is the same. The mere contiguity does not necessarily afford any proof, but it greatly simplifies the statement of the problem and the presentation of evidence. For the same reason as in the guinea-pig, the udder of the fœtal calf would probably be found very useful for putting this question to the proof. In a fœtal cow-calf, about half-grown, the udder is found to have its proper shape and its relative size, being a conical

eminence completely raised above the skin, upwards of an inch in diameter at its base, and somewhat less in height. Two pairs of teats are also perfectly developed, and the rudiments of large ducts or lacunæ are found over a small space directly beneath the teats. The substance of the udder is a gelatinous mass, in the midst of which lie a large number of small round bodies of a somewhat different texture, like tubercles in the substance of an organ. These round tubercle-like bodies are distributed throughout the whole substance of the udder quite regularly, and it might be supposed that they were the already developed lobules of the gland, visible through the gelatinous stroma. On examination, however, they are found to be collections of fat-cells, developing from the gelatinous embryonic tissue of the udder at many regularly distributed centres. The abundant gelatinous tissue in which they occur is of the embryonic kind usual in the mesoblast, containing numerous spindle-cells and a large amount of hyaline intercellular substance. The hypothesis, as regards this form of udder, would be that the acini develope throughout the whole udder from the remaining embryonic tissue, in much the same way, and from a corresponding number of independent centres, as the fat-lobules had done before them. It was not possible, however, to put the hypothesis to the test, from want of suitable material.

In describing the development of the mamma in the guinea-pig, it is convenient at first to assume the development of the ducts, and to consider the acini apart. In Fig. 2 is shown a portion of a duct and terminal branches. The tissue surrounding it is a part of the embryonic tissue that the whole wedge-shaped body in the groin at one time consisted of. The ducts now penetrate the centre of it, and the fat-tissue lies immediately outside it. Those surviving tracts of embryonic tissue are seen to contain groups of cells at various points, which, at first sight, resemble the aggregates of embryonic cells that the fat-lobule had developed from. Turning now to Fig. 1, showing the state of the mamma two or three weeks later, the place of the embryonic tissue round the duct is found to be taken by a large collection of acini, completely overshadowing the central duct to which they are related. The rudimentary or potential lobule of the earlier period has expanded into a voluminous group of acini, each of which resembles rather a small collection of fat-cells than the epithelium covered recess of a

secreting gland. The acini are essentially collections of fat-cells which have developed from the remaining tracts of the matrix-tissue by the side of the ducts, and which have undergone exactly the same process of transformation in the individual cell that the fat-tissue had undergone at an earlier period. The original wedge of embryonic tissue in the inguinal region has become fat-tissue, except along certain central tracts or planes in which the already-formed ducts lie; the ducts, and the embryonic tissue among which they lie, form, as it were, an island of the original matrix that has escaped becoming fat-tissue. At a later stage of development, the encroachment of the fat is still greater, and the embryonic tissue remains only as narrow strips along the sides of the ducts and round their terminations. It is from these narrow margins of the original matrix that the acini develope. The great expansion of acini shown in Fig. 1 implies a very considerable development from so narrow a basis; but the process of expansion becomes intelligible by observing the mode of development in a single acinus. It is here that the observations now to be recorded agree with the general conclusions on gland-development arrived at by Goodsir.

If, in new-born guinea-pigs, the margins of embryonic tissue which run along the sides of the ducts, or extend from the ends of them in narrow planes through the fat, be examined closely, there will be frequently seen the appearances drawn in Fig. 4, *A*, *B*, and *C*, under a magnifying power of about 600 diameters. There is first distinguished a small cluster of cells, as in *A*; one of the cells is vacuolated and has a large nucleus on the periphery, two other cells have a conical extension of protoplasm, and there is on the other side an elongated nuclear cell. In the margin of tissue by the side of the duct, these four cells are a distinct and isolated cluster. This margin of tissue can be seen, by careful examination, to contain many such, and among them groups of the kind shown in *B*. This group is more obviously an independent cluster or colony; the outer row of cells have an elongated crescentic form, and some of them have processes which appear to complete the circuit and retain the whole within a definite boundary. In *C* a similar appearance is shown; the cellular development is found in the midst of one of the narrow strips of embryonic tissue that extend from the duct through the fat. At the lowest part of the

figure is a cluster of very minute nuclear cells; above them are two other rudimentary acini with better marked characters. The lower of the two contains two large vacuolated cells, not distinguishable from fat-cells; the resemblance to fat-cells is the same that occurs in the later stage of development (Fig. 1), and the groups of vacuolated cells are as clearly a part of the mammary structure in the one case as in the other. It appears probable that the regular spherical arrangement of the cells that form an acinus is produced by means of the extensive vacuolation of one or more of the cells. The periphery of the vacuolated cells represents the circular boundary of the acinus. If the figures *B* and *C* are compared, the crescentic cells in *B* that form the boundary of the acinus will be found to correspond to the peripheral nuclei of the large vacuolated cells in *C*. All the cells of the cluster, more or less, undergo the vacuolation at one time or another; the earliest vacuolations seem to determine the form and expansion of the acinus, while in the acini of Fig. 1 the process is seen to be quite general throughout the large number of cells that the acinus now contains. These appearances, apart from their bearing on the homology with the fat-lobules, seem to point to a less rigid law of acinous development than that laid down by Goodsir. According to Goodsir, "an acinus is at first a single nucleated cell. From the nucleus of this cell others are produced. From these, again, others arise in the same manner. The parent cell, however, does not dissolve away, but remains as a covering to the whole mass, and is appended to the extremity of the duct. Its cavity, therefore, as a consequence of its mode of development, has no communication with the duct." According to this view, based chiefly on studies of invertebrate or lower vertebrate animals, the boundary of the acinus is formed by the distended wall of a single cell, in the parent cavity of which all the cells of the acinus, or the future epithelium, have developed. However that may be, the present description agrees with that of Goodsir in the important point that the development of acini is not by means of protrusions of the ducts so as to form infundibula or recesses at many points along their course, but that it is an *interstitial development* from the embryonic tissue that surrounds the ducts. Those margins of embryonic tissue, it has been said, become extremely narrow by the time that the system of ducts and the surrounding fat are

completely developed; so much so, that at some places they might be maintained to be nothing more, in relation to the ducts, than a submucous row of cells. In that point also there is an agreement with the observations of Goodsir, and it will be seen from the quotation that he did not find the circumstance just mentioned to be inconsistent with the notion of interstitial development. The observation of Goodsir does not refer to the embryonic development, but to those periodical "developments" of glands from season to season, which he compared to their embryonic development. The example chosen is the testicle of a shark (*Squalus cornubicus*) in its various stages as it advanced from the resting state to the active secretory state at the time of sexual vigour. The "development" of the acini had the following stages:

"1st. A single nucleated cell attached to the side of the duct, and protruding, as it were, its outer membrane.

"2nd. A cell containing a few young cells grouped in a mass within it; the parent cell presenting itself more prominently on the side of the duct.

"3rd. A cell attached by a pedicle to the duct, the pedicle being tubular and communicating with the duct; the cell itself being pyriform, but closed and full of nucleated cells.

"4th. Cells larger than the last, assuming more of a globular form, still closed, full of nucleated cells, and situated more towards the surface of the lobe.

"5th. The full-sized vesicles already described as situated at the surface of the lobe. These vesicles are spherical, perfectly closed; that part of the wall of each which is attached to the hollow pedicle forms a diaphragm across the passage, so that the vesicle has no communication with the ducts of the gland." When the contents of the acini are mature, the diaphragm, says Goodsir, is broken through, and the contents of the acini are discharged into the ducts.

Having described in the guinea-pig the mode of origin of the acini by the side of the ducts, and their appearance in a fully-expanded lobule at the time of birth, it will now be possible to trace the parallelism with the fat-development at all points. The cluster of four cells in Fig. 4, *A* (mamma of guinea-pig), is in every respect the same as those small groups of cells that indicate the beginning of a fat-lobule in the extreme inguinal region of the

fœtal kitten; the presence of one or more vacuolated cells, around which the others are grouped, is no less characteristic of the latter than of the former, and this initial similarity is as striking as the resemblance at more advanced periods. In the case of the kitten, these "germinal spots" of the matrix proceed to form the lobules of a fat-body, which has many points of resemblance to a gland; in the case of the guinea-pig they arise by the side of a system of ducts *already there,* and instead of forming a gland-like fat-body, they become the serviceable acini of a racemose gland. The stages A, B, and C of Fig. 3 (fat-lobule of kitten) may be compared to *A, B,* and *C* of Fig. 4 (mammary acinus of guinea-pig); while the expanded mammary lobule of Fig. 1 may be compared to a cluster of fat-lobules of the same gland, as they existed three weeks earlier. There is thus an identity as regards the matrix-tissue, a similarity in the initial grouping of the embryonic cells, and a similarity in the destiny or subsequent transformations of the cells, that can hardly fail to arrest the attention. That destiny is that they become spherical, assuming a protoplasmic investment round the nucleus, and that they undergo a process of vacuolation. The two distinguishing features of the groups of cells that become the mammary acini may be said to be, (1) that they are the last of the embryonic cells to undergo their peculiar development, and (2) that they are ranged along the sides of ducts. In those two circumstances lies the differentiation, in the individual development, of the mammary acini from the other parts of the fat-body or of the inguinal fat-region. The comparative anatomy of the breast will throw some light on the way in which that differentiation has originated. It will be convenient to introduce this subject at once, in treating of the next section of the inquiry, viz. the development of the ducts.

In the guinea-pig a system of ducts is found extending throughout the entire region of the future gland at least two weeks before any acini can be distinguished as such, and both in the fœtal kitten and guinea-pig the nipples are well formed at a still earlier period. This order of development in the individual rodent or carnivorous animal is a remarkable reversal of the order of appearance of the various structures in the phylogenetic succession of mammalian animals. In the *Ornithorhynchus* and *Echidna* there is no nipple, and there are, strictly speaking, no ducts. The

mamma is composed of about 100—200 flask-shaped follicles, each of which terminates in the skin by an elongated neck. The necks into which the follicles are drawn out, and by which they are attached to the skin, may be regarded as an incipient system of ducts. In each follicle there does not appear to be more than a single central passage. The gland, in fact, belongs to the follicular order of glands, which appear to be the primitive type of secreting structures, and which often occur in the lower animals where higher species have glands of the acinous type. The follicles are generally elongated, the blind extremity being slightly pointed. The substance of the follicle is a mass of secreting cells, in whose midst a more or less regular passage exists near its attached end, by means of which the secretion is poured out. It has, indeed, been asserted by Owen[1] that the structure of the gland in the *Echidna* is "on the same general plan as that of the mammary glands in higher mammals," and he states, in particular, that the duct by which the follicle or lobule opens on the skin is "directly continued from a canal which may be traced about half way towards the fundus of the lobule; the canal gives off numerous short branches from its circumference, which subdivide and terminate in clusters of sub-spherical 'acini' or secerning cellules." He also states that the structure closely resembles that of the *Ornithorhynchus.* I have taken the opportunity of examining the minute structure of the glands of both animals with reference to their alleged acinous type. That of the *Echidna* was in its most fully expanded state, while that of the *Ornithorhynchus* was in an extremely "involuted" condition, and had not one-tenth the volume of the other. In former chapters I described at length the histological nature of those periodical processes of "evolution" and "involution," and among other noticeable points was this, that in the full development of the secreting structure during lactation it was difficult to see the system of ducts on account of the great expansion of the acini which concealed them, while in the shrunken or involuted state of the gland, when the function was in abeyance, the ducts and clusters of terminal acini were everywhere prominent, and their branching arrangement could be clearly traced. So that, if the microscopic examination revealed no system of ducts and ter-

[1] *Philosophical Transactions*, 1865.

minal acini in the expanded gland of the *Echidna*, they ought at least to have been quite visible in the involuted gland of the *Ornithorhynchus*. But such was not the case. A single central passage ran through each lobule, and it is probable that it had, when fresh, a lining of columnar epithelium; but a racemose system of ducts and acini was certainly not present. The minute structure of the mamma in those two animals will be briefly referred to afterwards; for the present they may be considered without doubt to be glands of the follicular type. The class of animals that come next to the *Monotremata*, as regards the simplicity of the breast-structure, are the *Cetacea;* the marsupial animals in this respect must be considered somewhat higher. In the porpoise each gland has a single common duct, which runs from a reservoir under the nipple downwards to a considerable depth. Around this central vertical duct the secreting follicles of the gland are grouped in more or less horizontal planes at various depths. The structure is still essentially follicular, but the follicles, instead of opening on the skin each by its own duct, discharge into a common conduit at various points[1]. It may be shown diagrammatically how the racemose system of ducts could be produced by extending the same principle of centralisation, of which the beginning is seen in the cetacean mamma. With the racemose system of ducts comes necessarily a subdivision of the parenchyma into acini. It is perhaps impossible now to trace, in nature, all the steps by which this modification came about, but it appears certain that the original part of the mamma was its parenchyma, or the solid aggregates of its secreting cells, and that the ducts, which greatly help to economise the secretion, were acquired later. Now, as regards this particular organ of the body, the principle that the embryonic development in the individual is a brief recapitulation, in their order, of all the acquisitions that have been made in the phylogenetic succession, does not hold good. The nipple is the latest addition or improvement on the original mamma, but in the guinea-pig and cat, and no doubt in animals generally, it is developed in the skin long before the secreting structure is developed in the lower stratum. The elaborate system of ducts constitutes the

[1] The resemblance of the cetacean mamma to that of the *Ornithorhynchus* was pointed out by Von Baer during the controversy that followed Meckel's discovery of the gland in the monotreme.

other addition or improvement, but in the guinea-pig the plan of them is laid down throughout the whole extent of the future gland, before the essential secreting structure or parenchyma makes its appearance as such. The early appearance of the ducts has been duly noticed by the writers on the development of the breast, and it is no doubt owing to the circumstance of the ducts appearing first in the individual, growing as it were from the *rete mucosum* downwards, that the gland has been taken to be essentially a complex reduplication of the ectoderm, the recesses or infundibula of which were utilised for secretion. It has been pointed out, at the beginning of the chapter, that the theory had been accepted without due consideration of the defective kind of evidence on which it was based; and in describing particularly the development of the acini or the essential secreting part of the gland, I have been led to an entirely different view of the development of the whole organ.

But the question then remains, How comes it that this alleged order of acquisition of the various parts of the mamma in the evolution of animals, is reversed in the development of the organ in an individual of the higher mammalians, such as the guinea-pig? In answering this question it will be necessary to make use of an argument that is expounded in Mr Herbert Spencer's *Principles of Biology,* and which appears to be an original generalisation of that writer. The following extract[1] will present the argument in the briefest possible way.

"The same kind of structure is not always produced in the same ways; and some allied groups of organisms have modes of evolution which appear to be radically contrasted. The two modes are broadly distinguishable as the *direct* and the *indirect.* They may severally characterise the general course of evolution as a whole, and the course of evolution in particular organs.... Thus in the immense majority of articulate animals, metamorphoses, more or less marked and more or less numerous, are passed through on the way to maturity. The familiar transformations of insects show us how circuitous is the route by which the embryo-form arrives at the adult form among some divisions of the *Articulata.* But there are other divisions, as the lower *Arachnida,* in which the unfolding of the egg into the adult

[1] *Principles of Biology*, Vol. I. p. 371 et seq.

takes place in the simplest manner: the substance grows towards its appointed shape by the shortest route."

The general rule is that the indirect development characterises the most highly organised forms; conversely it is direct in a large proportion of the lower types. One of Mr Spencer's illustrations from social affairs is the following:

"A new town in the United States arises not at all after the old method of gradual accumulations round a nucleus, and successive small modifications of structure accompanying increase of size; but it grows up over a large area according to a predetermined plan; and there are developed, at the outset, those various civil, ecclesiastical and industrial centres, which the incipient city will require."

The argument then proceeds:

"Now on the hypothesis of evolution, all organs must have been originally formed upon the indirect method, by the accumulation of modifications upon modifications; and if the development of the embryo repeats the development of ancestral races, organs must be thus formed in the embryo. To a considerable extent they are thus formed."

Mr Spencer then gives examples of organs that are formed according to the indirect mode, and of other organs formed according to the direct, and concludes that, on the hypothesis of evolution, the direct mode of development in the latter class must have been substituted for the indirect.

The bearing of this speculation on the development of the mamma and its various parts, will now become apparent. As there are certain classes of animals distinguished from other classes by the "directness" of their development, and as there are some organs so distinguished from other organs in the same animal, so there are, in one and the same organ, some parts developed "directly" and other parts developed "indirectly." In the mammary gland, the nipple and ducts are developed directly, and the secreting structure, or the acini, are developed indirectly. In a mammary gland, the ducts were originally spaces formed in the midst of the parenchyma by a modification or adaptation of the same along certain central tracts. But the developing gland in the individual (guinea-pig, for example) does not repeat the particular steps of adaptation or modifica-

tion, inasmuch as the ducts are laid down throughout their whole extent before the secreting structure appears. The indirect process of adaptation is replaced by a direct mode of origin. It will now be suitable to introduce certain facts relating to the origin of the ducts.

In the wedge-shaped body of embryonic tissue in the groin of a fœtal guinea-pig less than half grown, but with nipple already formed, there are seen, extending backwards from the nipple, certain narrow tracts of cells, which are simply the embryonic cells of the part closely packed together. These tracts of closely packed cells form at various points throughout the embryonic mass independently of each other, and no continuous extension of them can be traced from the nipple. At this period of development, the fat-lobules are beginning to form from the same matrix, and it is difficult in some cases to distinguish the elongated and narrow collections of rudimentary fat-cells from the first mentioned linear aggregations of cells. But there are some unambiguous cases in which a distinct lumen can be seen in the narrow tract of cells, both in the longitudinal and in the cross section, and it can hardly be doubted that these are rudimentary ducts. The appearances observed in the udder of the fœtal calf, and in the mammary region of the new-born rat, also favour this view of the origin of the ducts. There is certainly no evidence of a process of growth downwards from the rete mucosum under the nipple. The mode in which a communication is formed between the epidermic excavation or depression in the nipple, and the ducts forming in the lower stratum, does not seem to present any great difficulty of explanation.

The ducts are therefore held to be formed as aggregations of the embryonic cells of the matrix along certain predetermined lines; that preliminary point may be taken as established, and it matters little for the present purpose that no circumstantial account can be given of the manner in which these cord-like structures are formed into hollow tubes lined, in the mature state, with columnar epithelium. Certain facts of a negative kind can however be made out. In the course of formation of the ducts, the embryonic cells do not appear to undergo any of the very marked transformations that have been described for the

cells of the acini. As compared with those other structures that the matrix-tissue gives origin to, the ducts may be said to be formed out of the embryonic cells by the "direct" mode. In Mr Spencer's words, "the substance grows towards its appointed shape by the shortest route." It is this shortened or direct mode of development that must be held to explain the early appearance of the ducts. But the question still remains, how it is that in the case of the ducts their development is by the direct, and not by the indirect mode. This brings us back to Mr Spencer's question: "How comes the direct mode of development to have been substituted for the indirect?" It will here be necessary to resume the quotation from Mr Spencer.

"Supposing it were possible for a race of organisms to have continued propagating itself through an indefinitely long period without any change of conditions necessitating change of structure; there would be reached so complete a congruity between the organic aggregate and its physiological units, that the units would arrange themselves directly into a structure like that of the adult organism: the germ would put on the proper characters of the species with little or no transposition of substance. But in the absence of any such constancy of conditions and structure, what may we expect? We may expect that where the conditions and structure have been most constant, the mode of development will be the most direct; and that it will be the most indirect where there have been the greatest and most numerous changes in the habits and structures of ancestral races of organisms...Between different parts in the same embryo, there are unlikenesses in the method of formation, which seem to have kindred meanings."

The former part of Mr Spencer's argument was made to apply to different parts of the same organ, and it will now be seen how the reasoning of the last quotation applies to the different modes of development within the mamma.

Comparing the parts of the mature mamma with one another, the ducts are those parts that exist throughout the life of the individual "without any change of conditions necessitating change of structure;" whereas the secretory activity of the gland depends on constant changes in the cells of the acini. This fact cannot be better illustrated than by reference to the

periodical processes of "involution" and "evolution" described in the first and second chapters. In those processes the ducts alone continue as they were during the state of active lactation; the whole processes of upfolding and unfolding take place in the acini or true secreting parts of the gland. The ducts play a purely mechanical part, and they continue without change from the time that their development was completed. According to Mr Spencer's argument as extended, it is under such circumstances as these that the direct mode of development is substituted for the indirect; and it would appear to be in accordance with this principle that the ducts of the mamma, though they are additions to the primitive mamma and acquired comparatively late in the succession of mammalian animals, are in the individual higher mammalian developed from the matrix-tissue of the gland before the secreting structure itself. To borrow Mr Spencer's illustration of a modern town of rapid growth, the ducts of the breast are like the roads and streets that are laid down before any houses are built. In the primitive state of a community, dwellings came first and streets afterwards; in the primitive condition of the breast, the secreting follicles of the gland existed first, and in course of time they became connected together by a system of ducts.

The conclusions of this inquiry are:

(1) That the mammary acini of the guinea-pig develope at many separate points in a matrix-tissue; that the embryonic cells, from which they develope, are of the same kind that give origin to the surrounding fat-tissue; and that the process of development of the mammary acini is step for step the same as that of the fat-lobules.

(2) That the ducts of the mamma develope from the same matrix-tissue by direct aggregation of the embryonic cells along predetermined lines; that the ducts develope in the individual guinea-pig before the acini, whereas in the phylogenetic succession the ducts are a later acquisition; and that this reversal of the order of acquisition of parts is in accordance with the principle stated by Mr Herbert Spencer that, under certain circumstances, the *direct* mode of development tends to be substituted for the *indirect*.

EXPLANATION OF PLATE.

Fig. 1. Section from the mamma of a guinea-pig four days old. A rounded or pyriform lobule made up of a large number of acini, the cavities of which are distended with vacuolated cells. Nuclei are to be seen among the vacuolated cells at various depths. × 300.

Fig. 2. Section from the mamma of a fœtal guinea-pig about three weeks before birth. System of ducts surrounded by embryonic tissue. × 300.

Fig. 3. Showing the development of a fat-body.

A. From the gelatinous tissue in the inguinal region of a fœtal kitten $2\frac{1}{2}$ inches long. In the middle of the figure, a small group of the embryonic cells undergoing changes to become fat-cells. × 300.

B. From the gland-like tissue in the same region of a fœtal kitten $3\frac{1}{2}$ inches long. Later stage of the fat-lobule. × 300.

C. From the fully-developed fat-body in the inguinal region of a new-born kitten. A small lobule of the fat-body, showing the vacuolated condition of the cells. × 300.

Fig. 4. From the mammæ of new-born guinea-pigs. × about 600.

A. Group of four cells in the embryonic tissue at the side of a duct. The earliest appearance of an acinus.

B. Similar group showing a later stage of the acinus.

C. The upper part of the figure shows two acini developing in the midst of a tract of embryonic tissue. Several of the cells extensively vacuolated.

Fig. 1.

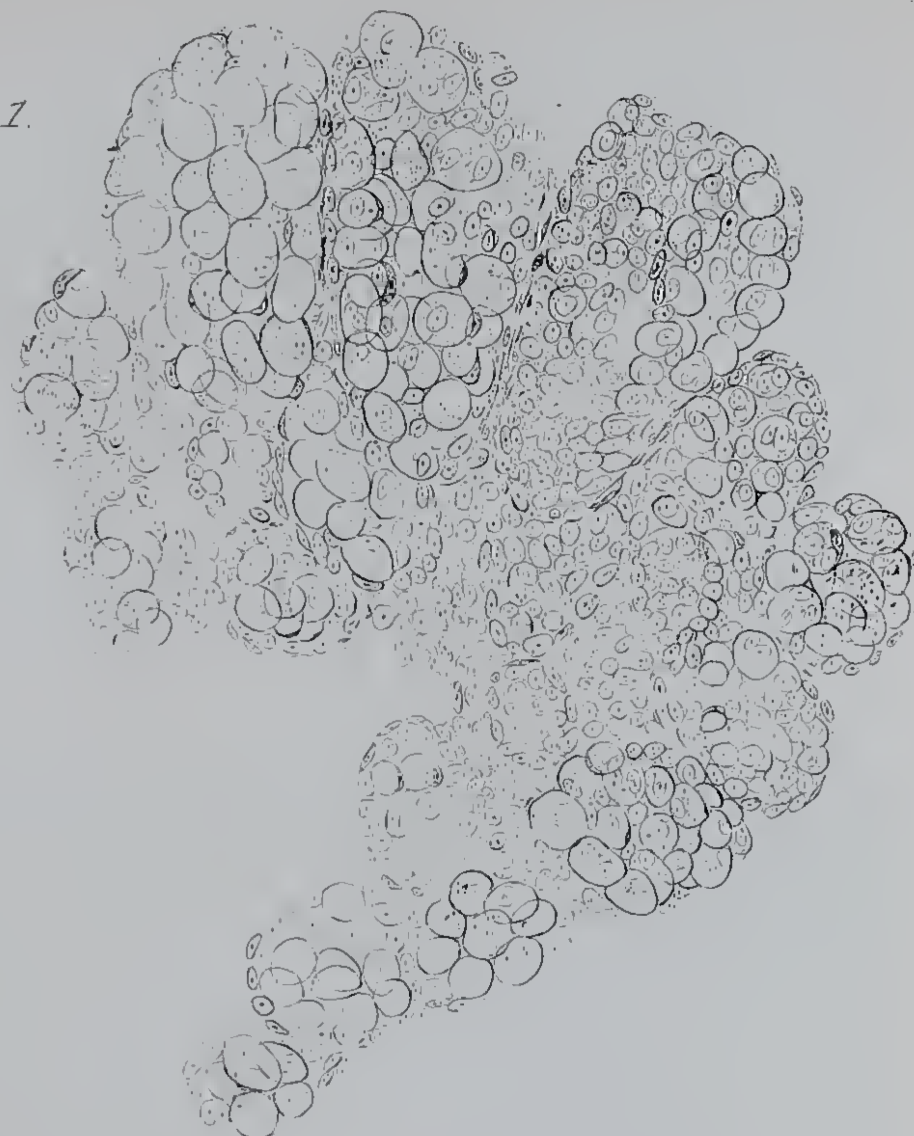


Fig. 2.

Fig. 3.

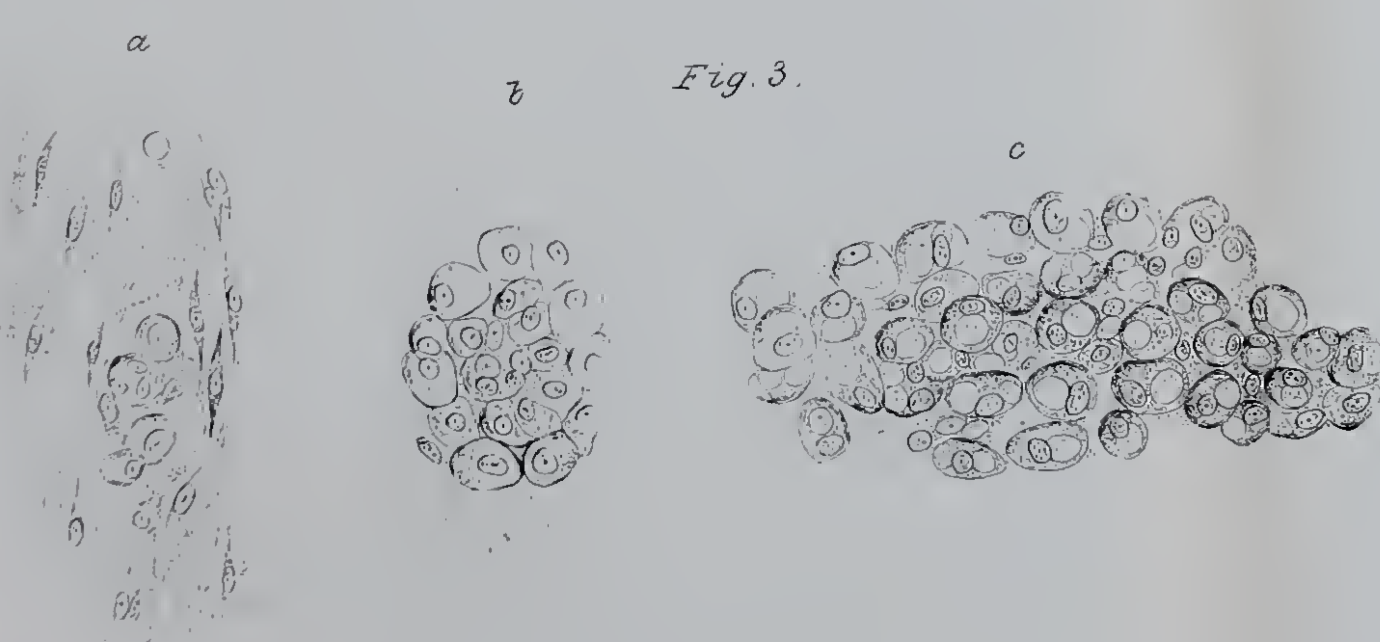


Fig. 4.

C. Creighton. delt.

T P Collings.

CHAPTER V.

THE DEVELOPMENT OF THE MAMMARY FUNCTION.

THE development of function is one of those interesting departments of physiology that the modern teachers of the science do not profess to include in their programme. It is remarked by Haeckel that "the physiology of to-day does not concern itself either with the functions of development or with the development of functions. In its very one-sided tendency, it strives to bring to the highest degree of completeness our knowledge of single groups of functions—for example, the physiology of the organs of sense, of muscle, of the circulation, &c.—while there are other functions for which it has no concern." And he enumerates certain functions of the organism that are not included in the scope of physiology, as it is defined by the works of its professed teachers[1]. I must leave such criticisms to those who can make them with due authority, and, in a volume of mixed contents like the present, I may treat of one of the neglected subjects in question, without inquiring too curiously whether its interest is for physiologists or for others. The consideration of most practical importance is that one finds no classical writings on the development of function, and it is therefore with some diffidence that I attempt, under an explicit title, to treat of the development of the function of a particular organ.

The breast is an organ on which the experiment may at least be advantageously tried. Compared with an organ like the liver,

[1] *Anthropogenie*, p. 130.

compared even with an organ like the lachrymal gland, it appears late in the succession of animals. It may in fact be considered to be the latest acquisition or addition to the glandular system of animals. Moreover, in the class to which it is confined and for which it supplies the class-name, it exhibits the more simple type of gland-structure at one end of the scale, and the more complex type at the other. The first part of this chapter will treat of the development of the mammary function in so far as it may be deduced from the character of the gland in the *Monotremata;* in the second part, the development of the function will be considered with reference to the cellular processes by which the gland takes origin in the guinea-pig, and their parallelism with the cellular processes in the functional periods of the mature organ.

From the observations of Mr G. Bennett, made on the living animals in Australia, there seems little doubt that the gland of the *Ornithorhynchus* does secrete some kind of milky fluid at a certain time of the year. Mr Bennett has seen the milk exuding on the skin, in a manner which reminded him of Owen's description of the exudation of the mercury that he had injected into the substance of the follicles from their free extremities. He records, however, the following exceptional case: "This female had evidently just produced her young, and the uterine organs exhibited no appearance of any more being likely to be brought forth. The mammary glands on each side were very large; but it is a curious and rather interesting circumstance in the economy of this animal, that after having been shot, no milk could be expressed from the glands. This was the more surprising to me, as the glands were very vascular on the surface, the mammary artery ramifying over them in a most beautiful and distinct manner. The fur still covered that portion of the integument on which the ducts terminated, and there was no appearance of a projecting nipple. In the animals which I have subsequently seen with a lacteal secretion, there has been no projecting nipple, and the fur is not even invariably found quite rubbed off at the situation where the ducts of the gland have their termination[1]."

The gland is subject to the same periods of activity and rest as in the higher mammals; but the utilisation of its secretion is

[1] *Transactions of the Zoological Society*, Vol. I. p. 251.

so obviously uncertain that one is entitled to dismiss altogether the teleological idea of a secretion, and to consider the activity of the organ rather as being correlated to that of the other sexual organs, and ultimately to the season of the year. The full expansion of the organ is found only in the specimens procured about the month of December; Mr Bennett's specimens shot in August had the gland in the state of extreme contraction, and it is generally found in that condition in the specimens that are sent to this country.

The gland in its contracted state has perhaps less than one-tenth the volume of the state of full expansion. The hundred or more independent follicles of which it consists are small oat-shaped bodies of a brown colour, about four or five lines long, and a line in breadth at their middle. They are arranged in the form of a fan, with their necks converging to a narrow linear space under the skin about one-quarter of an inch in length. At that point there is an ill-defined break in the *panniculus carnosus*, and the necks, or rather the upper pointed ends, of the follicles appear to lose themselves in the subcutaneous tissue. When the fur which covers that region—equally with the surrounding skin—is completely scraped off, the skin to which the follicles converge shows, under a lens, no obvious differences from the rest of the skin. The mouths of ducts cannot be detected, nor any other openings than those of the hair-follicles. In microscopic sections through the whole thickness of skin and through the length of the attached follicles as well, no passages resembling ducts are found traversing the skin to its surface. I have made sections of the involuted gland in a direction exactly perpendicular to the skin, throughout almost the whole region where the follicles were attached. The collected ends of the follicles, owing to their brown colour, could be seen, with the naked eye, to end in the corium like a rounded papilla, the follicles in the centre of the convexity coming nearest to the surface. Under the microscope I could trace no obvious communication with the skin from any one of the numerous follicles that the section encountered. Ducts with an epithelial lining could hardly have escaped notice, although the gland, from long keeping in spirit, did not afford very reliable histological appearances. So far as the follicles of the shrunken or involuted gland are concerned, they appear simply to end in the corium

with pointed processes. In the absence of better histological evidence, it may be stated as at least probable that the discharge of the secretion on the surface depends not on the presence of permanent ducts, but rather on a kind of transudation through the skin, caused by the accumulation of fluid products in the organ during its period of extreme expansion[1].

The conclusion arrived at in the last chapter was that the homologue of the breast is not a cutaneous gland, or, at any rate, that it is not a recess of the skin; but that it is a fat-body. The primitive condition of the breast that is found in the *Monotremata* may be described, without greatly straining the facts, as a fat-body whose lobules converge to a particular limited area of skin. The follicles of the gland in the female *Echidna* have, in their state of full expansion, the most curious resemblance to fat-lobules[2]. There is the special feature of a central passage in each follicle, and round it there are grouped the subdivisions or compartments of the structure. Each of the compartments has its walls as it were honey-combed with saccules or vesicles, which differ from the vesicles of fat-tissue chiefly in their being often much smaller,

[1] In dissecting a male specimen of *Echidna hystrix*, which was placed at my disposal by Mr F. M. Balfour, I discovered, in a cleft of the *panniculus carnosus* towards the lower end of the abdominal wall on each side, a well-marked organ having the appearance of the involuted mammary gland of the female in miniature. The follicles were of the same shape and colour, and converged to a point in the subcutaneous tissue. I made sections, perpendicular to the skin, through the whole group of follicles and attached piece of skin, but found no trace of open communications between the pointed ends of the follicles and the cutaneous surface.

On examining the corresponding part of the abdominal wall in the male *Ornithorhynchus*, I found a still more rudimentary form of gland, consisting of only a few of the oat-shaped follicles. The existence of the mamma in the male monotreme has been overlooked hitherto, and Owen has based an argument on its assumed absence. In writing on the subject of this chapter in the *Journal of Anatomy and Physiology*, Vol. XI. p. 29, I took for granted that the mamma was absent in the male, and endeavoured to show, by a reference to the form of the mamma in male cetaceans, that the *glandula femoralis* of the male monotreme was the homologue of the mammary gland of the female. A speculation to the effect that the mamma was first "acquired" by the male animal was based upon the supposed homology. The theory and speculation naturally fall to the ground, as theories and speculations often do. I hope to include an account of the mammary glands of the male monotremes in a subsequent paper, along with a number of other new points relating to the glandular system of those animals.

[2] I am indebted to Professor Flower for the opportunity of examining this gland microscopically.

though many of them are as large as a well-filled fat-cell. The larger vesicles or saccules appear to have membranous walls, or to be divided from one another by membranous septa; the smaller vesicles suggest rather drops of fluid, and the central space of the compartment is often occupied by a vesiculated fluid. From its staining by logwood, the fluid appears to be of an albuminous or mucous nature. The gland from which the sections were made had been preserved for a long time in spirit, and was not well adapted to show certain histological points, such as the presence of nuclei.

Those resemblances between the expanded gland of the monotreme and what may be called the usual condition of fat-tissue are by no means slight. But it is more striking to find that the differences between the gland in its expanded state and in its contracted state are the same as the differences between the fat-body, say of a frog, in its spring condition and in its winter condition. When the contracted or resting state of the gland of the monotreme is compared with its expanded state, the difference is found to be not only in the volume of the organ, but also in the character of its component cells. The compartments into which the lobule or follicle is subdivided are retained in a reduced shape, and the septa between them appear relatively thick. But the cells that lie in the compartments are not the large vesiculated cells, or the honey-comb aggregates of membranous saccules, but round granular and nucleated cells, without a cell-wall, and filled with yellowish-brown pigment. Each space of the follicle contains only a few cells, and they lie in the space without any regular arrangement.

The differences between the cells of the organ in its expanded condition and in its state of contraction resemble the differences between the ordinary fat-cells and the so-called atrophied fat-cells. The amount of pigment that is dissolved in the fat varies in different animals, and the colour may range from yellow to red, and among the invertebrata to more unusual colours. When the fat disappears from the cell, the pigment remains behind in the cell-substance in the form of a granular mass[1]. The atrophy and expansion of fat-bodies, or of the fat in certain regions, is a periodical process which generally follows the sexual

[1] Toldt, *Lehrbuch der Gewebelehre*, 1877, p. 44.

periodicity of the animal, that is to say, the periodicity of the seasons. In the last chapter I quoted the opinion of Toldt as to the essentially glandular character of fat-bodies; their periodicity is another point that brings them into comparison with the accessory sexual glands. They differ from ordinary secreting glands in so far as they have no mechanism for the discharge of a secretion; and the mammary glands of the *Ornithorhynchus* differ in the same way, though in a less degree. In the latter organ, the system of passages within the gland is of the most primitive kind, the communication between the cavity of the follicle and the surface of the skin is not at all obvious and may be nothing more than occasional, the skin of the mammary region is not even denuded of its fur, and the collection or utilisation of the secretion is manifestly precarious. From all these considerations it appears to me that the mammary glands of the *Ornithorhynchus* may be described with equal justice as somewhat specialised fat-bodies. The specialisation must be sought for in several points, but the earliest and least intelligible step in the process of adaptation is the centripetal grouping of the follicles or lobules.

In considering the development of the glandular function through the line of a homology with fat-bodies, the chief physiological factor must be held to be that of periodicity. It is the periodical expansion of the fat-lobule that brings with it the fluid contents of the cells, and it is the periodical expansion of the mamma in the monotremes that issues in the formation and discharge of a secretion. Whatever may be the ultimate causes of periodicity within the organism, it appears sufficiently obvious that, both in plants and animals, their periodicity depends in a general way upon the round of the seasons. As periodicity appears to be the most primitive character of certain physiological processes, in like manner may the presence of this grand factor be traced in the development of function in the individual embryo. The developmental process of the mamma is itself the first functional period of the organ. I shall occupy the rest of the chapter with an exposition of this statement.

I have shown, in the first and second chapters, that lactation always follows upon a slow unfolding of the secreting structure and a gradual rising of the secretory force. Lactation is the rising secretion maintained for a longer or shorter period at its highest

point. If a full period of the breast's activity be represented graphically, a line sloping upwards would represent the evolution, a line continued horizontally would represent the lactation, and a downward extension of the line would stand for the upfolding and subsidence. Lactation is the function of the organ continued for a time from its highest point at a uniform level; it is a period of variable length interposed—one may say, artificially interposed—between the original waxing and waning periods of the organ. It is not the unfolding and upfolding processes that are subordinate, but it is the period of lactation itself. The original law of periodicity is that "from hour to hour, we ripe and ripe, and then, from hour to hour, we rot and rot."

Turning now to the formation of the breast in the embryo, as described for the guinea-pig in the fourth chapter, the cells of the embryonic matrix in assuming the secreting structure will be found to exhibit a cycle of changes, which may be compared with the successive changes of a periodical evolution. The steps in the development of the acini are much more rapid than the prolonged stages of unfolding in the mature organ, and the parallelism cannot be observed at every point. But the beginning and end of the process are the same in both cases. The acinus, in the embryonic development, begins as a small group of embryonic cells, at first almost nuclear, but afterwards invested with a quantity of cell-substance. The next obvious change is a vacuolation of one or more of the group of cells, whereby the circular boundary of the acinus cavity is determined. At a later stage, all or nearly all the cells of the developing acinus are found to be vacuolated to such an extent as to resemble fat-cells. That condition corresponds to the highest point in the process of development of the acini. The vacuolated cells burst their membranous walls and discharge their contents; the discharged contents are *the milk of the newborn.* All the steps in that process are steps in the formation of the gland; the issue of the formative process is a discharge of milky fluid. The consummation of the process, indicated by the discharge of a fluid, corresponds, in some animals at least, to the time when the fœtus leaves the womb. The discharge of a milky fluid from the breasts of newborn children of both sexes is a very familiar observation, and I have observed the same occurrence at or a few days after birth in the animal to

which my description applies, viz. the guinea-pig. The fluid expressed from the nipple of the new-born guinea-pig had the appearance of a watery kind of milk; on microscopic examination, the milk-globules of ordinary milk were not found, but a more uniform fluid mass irregularly broken up under the cover-slip into large or small drops, and without any mixture of cellular elements. The ducts of the prepared gland often contained the same kind of fluid. After the acini have discharged the milk of development, they appear to contract their circuit greatly, and in young guinea-pigs at the beginning of their first pregnancy the acini are found in the same resting condition as in the adult, that is to say, they are small round spaces filled with a number of nuclei.

As the first pregnancy advances, the acini undergo the unfolding process that has been described in the second chapter, and when the term of pregnancy is ended, a fluid product is again discharged, this time in large quantity, and continuously for days or weeks as the case may be. It follows from these undoubted facts that the development of the breast is its first period, or that the functional periods of the mature breast are successive repetitions of its development. The conclusion is the same that is contained in one of the forgotten aphorisms of Goodsir. "We require renewed observations," he remarks, "on the original development of glands in the embryo. From the information we possess, however, it appears that the process is identical in its nature with the growth of a gland during its state of functional activity[1]."

I have already endeavoured to show that the continuous and useful production of milk, which alone constitutes the function from the physiologist's point of view, is not the essential or primary activity of the organ, but a mere prolongation of its evolutional force at its highest point. It is the periodicity of the organ that is its earliest characteristic, and that periodicity, as I make out, is the same as the expansion of a fat-body from season to season. The periodicity of the breast begins with the existence of the breast as a distinct organ; its development is its first period, and its subsequent periods are all repetitions of its development.

One may attempt to analyse, in various directions, the development of function as distinguished from the development of

[1] *Anatomical and Pathological Observations*, Edinburgh, 1845, p. 31.

structure. But that inherent union of structure and function, which is the grand characteristic of living things, is a dualism that cannot be resolved even in the study of development. In speaking of the periodical unfolding of the breast's structure and the correlated revival of its function, I remarked that one might find therein at least an illustration, although not an explanation of the union between structure and function. The one varied as the other varied; a low degree of function resided in what might be called a crude shape of cell, a high degree of function resided in what might be called a perfect shape of cell, and the intensifying of the function and the perfecting of the cell went hand in hand. In like manner the highest point or the last step in the development of the breast coincides with the discharge of a product, which is the type of its perfect secretion. The first fluid product of the breast is incidental to its development. Questions of heredity apart, the development is an ultimate fact; while secretion is a teleological idea. That which is incidental to the development becomes the secretion. The milk of development in the breast is the pledge of its future usefulness.

PART II.

PATHOLOGICAL.

CHAPTER VI.

PATHOLOGICAL PROCESSES OF THE BREAST.

In the first chapters I have described with considerable minuteness the various processes or modes of activity that are at work in the mamma of the female throughout the period of sexual maturity. So far as relates to the individual secreting elements of the gland, or to the behaviour of its cells as individuals, the physiology of the breast has been described with a certain amount of completeness. The cellular aspect of the physiology of an organ is never without its general interest; but for the morbid physiological action of the organ, that interest becomes paramount. It is only in a limited department of pathology, in the case of diseases such as gout and diabetes and the febrile state, that the chemical and physical subdivisions of physiology have a direct bearing. The grand disease of the breast is the tumour disease; and for the rational interpretation of the various departures from the normal of the organ that are included under that name, the account that has been given in previous chapters may be used as a sort of physiological key.

First among the physiological points that have been discussed is the fact of the periodical evolution and involution of the gland. No other organs of the human body, except the uterus and ovary, are subject to periodical changes of the same kind. The function of the breast intermits regularly for a longer or shorter period; its subsidence is gradual, and its re-establishment very much slower. In both of the processes the ordinary functional excitation of the gland is still present; but it acts at a lower degree of intensity, gradually decreasing to complete cessation in the involution, and

gradually rising to its full force in the evolution. In those two inverse processes there is a complete parallelism. They may be both divided into tolerably definite stages which correspond exactly in an inverted order. The stages are characterised by secretory products of the epithelium peculiar to them; and the peculiar secretory product of each stage, occurring as it does at corresponding periods of both processes, may be considered to be the characteristic product of the excitation of the gland acting at a certain absolute degree of intensity. When the functional stimulus of the mamma is acting at its lowest point, the secretory product is a large granular pigmented cell; if the mammary excitation were always to act at that degree of intensity, the secretion, it may be said, would be always in the form of large granular pigmented cells. At the next appreciable advance in the intensity of the stimulus, the product formed in the gland may be described somewhat generally as a large nuclear cell. Beyond the medium degree of intensity, the product is both fluid and cellular, the former being mucus and the latter, generally speaking, a small round cell. Coming still nearer to the full excitation, the cellular ingredients are fewer and the mucous production much more abundant. Finally, when the stimulus is at its height, the mucous fluid has given place to a fatty fluid, and whatever cellular elements the secretion contains are the well-known colostrum cells. This summary will be found to be strictly in agreement with the facts already detailed at length. It is submitted again that the parallelism between the involution and evolution processes is not at all strained, and that it is a legitimate inference to ascribe, in the abstract, a special kind of secretory product to a certain degree of intensity of the glandular force.

The various cellular and fluid products of the imperfect secretion are spoken of as waste products. The elaborate mechanism for the disposal and utilisation of the waste cells has been described in the third chapter.

Finally, and as a point of more theoretical interest, the law of the secretion, the *modus operandi* that is at all times implicitly present, and which is clearly manifested in certain of the imperfect states of the function, has been taken to be the law of endogenous cell-formation. It is with reference to the last mentioned and more theoretical of the conclusions drawn from the inquiry into

normal processes, that something remains to be said before passing to the diseased states of the breast.

The morphological differences between the endogenous mode of cell-formation and the mode by fission or division are on the whole well marked. Cell-formation by fission is essentially a partitioning of the whole parent cell into two or more fractions, which grow and acquire the same form and properties as the cell from which they came. Endogenous cell-formation is the production of one or more young cells within the body of the parent cell; the young cell rounds itself to a separate whole within a vacuole which contains also a certain amount of fluid substance. Cell-formation is the most elementary phenomenon of living things; and if there are varieties of cell-formation, it cannot be but that these varieties have a deep significance. Perhaps the two modes of cell-formation are not radically contrasted at all points; there are certainly phenomena of cellular activity that might be claimed for either of them. But the occurrence of ambiguous cases cannot be held as obliterating the distinction between them; and, on a broad survey of the facts, it seems admissible to conclude that well-marked varieties of the process exist.

Such then being the case, it will become, on consideration, a matter of some surprise that more has not been made of the varieties of cell-formation in the details of biological study; for variations in so fundamental a matter as the origin of cells must have a meaning. There is one particular laxity of thought and expression, running through many pathological writings and not altogether absent from biological, which is an example of the way that fundamental varieties of cellular activity have been overlooked. One of the most usual forms assumed by cells subject to the endogenous activity is that of a signet-ring. The cavity of the cell may contain nothing but fluid, the cellular element being on the periphery; and I have lately observed in preparations made from the granulation tissue covering a stump, that the periphery of the cell, corresponding to the stone of the ring, has contained not one nucleus only, but an enormous number of small nuclei. In other cases, the young cell or brood of cells lies within the cavity or vacuole of the parent cell. It so happens that the cells of ordinary fat-tissue exhibit the same appearances, chiefly in their development but to some extent also in their mature condition.

The fat-cell has come to be regarded by many writers as the type of all such appearances, occurring under whatsoever circumstances; and it has often happened that vacuolated cells, exemplifying the endogenous process, have from their resemblance to the common and, as it were, contemptible fat-cell, been summarily dismissed as examples of "fatty degeneration." It may be safely asserted that a large proportion of cells so described are neither fatty in their chemistry nor degenerating in their vitality[1]. If the practice were abandoned of referring all such vacuolar transformations of cells to one single and simple category of degeneration, there would be a better prospect of arriving at a true and rational generalisation of these manifold appearances.

Among pathological writers, Virchow has assigned an importance to the varieties of cell-formation that seems more adequate to the case. Under the name of *Physaliphoren* he describes and figures the usual varieties of vacuolated cells undergoing the endogenous process, and he applies that special name in order to distinguish them from cells, such as amœboid cells, that exhibit transient vacuolar appearances. The significance that I shall ascribe to the endogenous mode of cell-formation in the pathological considerations that follow, is the same that may be found in Virchow's writings, and is suggested by them. Contrasting the hyperplastic and the metaplastic or heterologous modes of growth, he observes, as regards endogenous new formation, that heterology characterises it from the outset, inasmuch as the elements produced in the mother-cell are as a rule small, apparently "indifferent" like granulation-cells, and predisposed to a devious course of development[2]. The property of metaplasia may be considered as belonging to the endogenous product under all circumstances; it may be said to inhere in all cells produced according to the law of endogenous cell-formation; and if we are content, for brevity's sake, to use a formula for the expression of the continuous series of processes in the breast that are not all obviously

[1] As regards actual fat-cells, or the cells of fat-tissue proper, a corresponding fixedness of idea prevails, and sometimes proves curiously inconvenient. Thus Flemming, while he correctly states the endogenous character of the phenomenon, describes the presence of a brood of young cells within the cavity of a fat-cell, and the associated disappearance of the fat, as an example of "growth-atrophy" (*Wucher-Atrophie*). Paradox can go no farther.

[2] *Cellular-Pathologie*, p. 492.

endogenous, we are at once led to the conclusion that all the cellular products of the secretion, or, in other words, the waste cells of the secretion possess the same property of metaplasia. It is in this property of metaplasia that their importance as regards disease chiefly consists. For metaplasia is nothing else than the heteroplasia which we uniformly associate with the "parasitism" or malignancy of tumours.

The tumour diseases described in this and the following chapters have been studied chiefly in the bitch. During a period of three years, I collected material from upwards of twenty cases of mammary tumours in the bitch, that were under treatment at the Brown Institution (hospital for animals), London[1]. I obtained also two mammary tumours from the cat. Although the tumours in the dog and cat differed in some respects from the ordinary mammary tumours in the human body, they had, as a class, the property of malignity equally well marked. Thus, in one of the cases in the cat, the tumour occurred as a circumscribed mass at a particular part of the chain of glands, and was removed by operation; there appeared, soon after, a fungus-like growth in the axilla and the animal died with numerous secondary tumours in the lungs. Several of the cases in the bitch ended fatally, and proved to have infection of the lymphatic glands with tumours in the lungs or liver. Most of the cases were operated on, and were not afterwards heard of; but three of the animals came under treatment a second time, the disease having broken out afresh, and over a larger extent of the gland. In about one-third of the cases in the bitch, there was the well-known tendency to the formation of cartilage at certain points; and in one case a large part of the principal tumour, but no part of the smaller nodules, was distinctly osteoid. But although a certain proportion of the cases showed a tendency towards the comparatively safe cartilaginous transformation, that tendency did not always exempt them from malignity. Thus, in an extensive tumour, removed from an animal that had undergone the same operation eighteen months before, there were found several small cartilaginous points; elsewhere the structure was of somewhat soft consistence, and the lungs were full of

[1] I am greatly indebted to Mr William Duguid, the veterinary surgeon of the Institution, for giving me the opportunities, from time to time, of making the collection of tumours, and for assistance in preserving them.

secondary tumours having the structure of the softer kind of tissue in the primary. A certain myxomatous character, of which the cartilaginous tendency may be considered to be a further development, was very generally present; one tumour (in a case where there were secondary growths in the liver) had a large cyst on its upper surface, filled with colloid fluid, and several of the cases differed in appearance from skirrhous cancers of the human subject chiefly in the brownish colour of the tumour juice. If the tumours of this collection were referred to their respective classes, there would be representatives among them of skirrhous cancer, medullary cancer, reticular cancer, alveolar cancer, cystic sarcoma, &c. I have introduced a brief account of eight cases of mammary tumours in the human subject, chiefly with the object of showing that they illustrate the same principles of tumour formation that I endeavour to establish from a more particular study of the cases in the bitch.

The cases in the bitch have the great and unique advantage for study, in that the tumour disease is often found in various stages at various points of the elongated chain of glands. Thus, in a particular case which ended fatally, there was one large tumour about two inches in diameter, and numerous small circumscribed nodules throughout the whole length of gland on each side; and, at one part, there was not so much a circumscribed tumour, but rather a uniform enlargement or thickening over the whole breadth of the gland and for a distance of about two inches longitudinally. In the animals that died or were killed I was able to secure the whole chain of glands with their numerous centres of morbid action; and in the tumours removed by operation I found, in almost every case, considerable fringes of more or less normal mammary tissue, which, though more troublesome to prepare, were hardly less valuable for the pathological inquiry than the entire chain of glands would have been. The material of the investigation included, therefore, not only tumours of the mamma, but also portions of the mammary tissue illustrating every stage of the tumour disease.

The attempt to refer the mammary tumours of the bitch to their respective classes, is here deliberately abandoned as serving no good purpose. It will doubtless be found to be more in keeping with the ætiological end proposed for the investigation, if the

attempt be made to find out what are the various starting-points of the diseased process from the normal. The first part of the investigation supplies, as has been said, a physiological scheme whereby to trace out and to estimate the extent of these abnormalities. The fringes of more or less normal gland substance, and the younger tumour nodules or enlargements form a kind of intermediate territory, in which the traces of healthy action are not altogether hopelessly obscured. It is in dealing only with this kind of material that one can hope to indicate the exact point of departure of the disease. There is indeed an infinite variety of appearances in the pathological mammary structure; there is nothing of it, one may say, but is changed "into something rich and strange." But those vagaries of nature may be reduced to a few leading principles. In the first part of the investigation we profess to have established one or more important laws of the healthy mammary activity, and the whole of the pathological investigation that follows will be found to be nothing else than an illustration of the working of those laws under altered circumstances. It is proposed, therefore, to give in the first instance a number of illustrations of morbid physiological action within the breast, and to point out from time to time the relation of the same to the various kinds of tumours.

The most common appearance in the more or less healthy mamma adjoining tumours, and in certain parts of the circumscribed tumours, is an appearance resembling that of the early evolution of the mamma. The figure No. 21 is taken from the mamma near a tumour. It is not at all different from the breast in the early stage of evolution, but there was no reason to suppose in this or in any other of the cases that the animal was subject to the ordinary cause of the unfolding of the breast from the resting state, viz. pregnancy. The effect, however, is the same; the acini are obviously subject to a certain degree of activity; they contain a number of the large yellow cells in their cavity and there is a considerable number of the same large yellow cells in passage through the loose fibrillar tissue outside. This appearance is constantly found in the bitch as the commencement of disease, and the process so far is a diseased process because the excitation to it is something other than the natural excitation to the evolution of the mamma. The gland is disturbed from its resting state and

proceeds to follow, to a certain point at least, the ordinary course of evolution. But, if one may so speak, it has been started along its wonted evolutional track on a false pretence. The evolution is spurious, and the end of it, as will be seen, is disastrous. Strictly

Fig. 21.

Lobule of a mamma near the resting state. Numerous large pigmented cells within the acini and in the interlobular fibrillar tissue; sections of three blood-vessels to the left of the lobule. Magnified 160 diameters.

speaking, however, the process is not one of evolution; it is rather the absolute effect of a certain low degree of excitation acting upon a gland in the resting state.

As we have already seen, the characteristic product of the lowest degree of excitation, whether at the end of involution or at the beginning of evolution, is the large granular pigmented cell. In the involution process, the excitation speedily comes to an end; the production of the large yellow cells is a passing phenomenon which the subsidence of the function gives few opportunities of observing well. In the evolution process it can be studied very much better; the cells are often found *in situ* within the acini, and large accumulations of them may be seen outside. But in the evolution also the phenomenon is transitory; the degree of the excitation is gradually increasing, and, for that or other reasons, the large yellow cells cannot be easily seen in what we must consider to be the successive steps of their career. In the cases of spurious excitation, however, the circumstances admit of the mode of production of the yellow cells being much more

deliberately observed. In the diseased process we realise partially that state of the secretion, corresponding to the third of Goodsir's "three orders of secretion" in the lower animals, where it does not advance to the production of milk, but continues all the time to act at a uniform low degree. The characteristic yellow cell is here a much more stable product, and, as will appear, sometimes

Fig. 22.

A pathological lobule. The uppermost acinus shows the pigmented cells as epithelium *in situ*. Magnified 160 diameters.

accumulates to form an epithelium of several layers. In certain cases the whole floor of an acinus has a yellowish tinge, a certain amount of pigmented substance being disposed round each nuclear cell. The acinus seen also in profile is found to have a complete circlet of yellow cells. Fig. 22 is a drawing of a portion of a lobulus of the mamma near a tumour. The lobuli near it are at

or about the usual resting state; they are smaller than the one figured, and separated from one another by the usual amount of fibrillar tissue. The whole of this pathological lobule has a distinct yellow tint, and the yellow colour of the cells in the half acinus at the top of the figure is very well marked. Their substance is the ordinary granular pigmented substance, but their form is peculiar. It is neither the round form of the normal pigmented cell, nor the polyhedric form of the perfect epithelium; but it is more of a columnar or club shape. Most of the cells in the other acini of the lobule belong to a class that will fall to be described afterwards. Fig. 23 shows a form of cell somewhat

FIG. 23.

From the mamma of a bitch, adjoining a tumour. The epithelium massed in more than one layer, or in villus-like processes. *The granular substance of the cells is everywhere bright yellow.* Magnified 300 diameters.

similar to that in the upper acinus of Fig. 22. The preparation is taken from the very much affected gland tissue round a tumour, and the striking point of the appearance is the brilliant yellow of the entire semicircle of cells. Where the cells are lying single they are found to be more or less columnar; elsewhere they are fused together into villus-like processes, consisting of a double row of three or four columnar cells on end. A more remarkable degree of the same kind of aggregation *in situ* of the pigmented cells is seen in Fig. 24. This is taken from the tolerably healthy gland tissue near a tumour. The portion represented in the

figure is evidently the recess of a duct, the epithelium of which shows the same characters as may be seen elsewhere within the acini of the gland. All the substance that is made to appear granular in the woodcut is in the preparation of a bright yellow.

Fig. 24.

From the mamma of a bitch, adjoining a tumour. Numerous villus-like processes of epithelial cells, growing from the recesses of a duct. *The cells are all pigmented yellow.* Magnified 150 diameters.

The two perpendicular sides of the recess have a border of yellow granular substance, which can be seen clearly enough at most places to consist of large cubical cells. From the bottom of the recess there springs a cluster of papillary processes, some of which

are cut obliquely and appear to be short, while two or three of them are long columns of uniform thickness, built up solely of large yellow granular cells arranged round a narrow central space.

In the class of appearances from which Figs. 23 and 24 are taken, there is evidently a great hyperplasia of the epithelium: the growth is almost vegetative in its characters. But the whole essence of the pathological process lies in the fact that there is more than a mere hyperplasia or excessive reproduction of epithelium. The yellow granular appearance of the cells is certain evidence that they are subject at the same time to the functional activity of the gland. It has been argued at some length in the physiological chapters that the formative activity of the mamma and the functional activity always go hand in hand. The formation of the secretion from successive sets of the epithelium presupposes constant relays of new cells, which, in the greatest activity of the function, are destroyed almost as fast as they are formed. What we have here is the formative excitation outrunning the functional. For whatever reason, the epithelial cells are not shed as soon as they undergo their degree of functional transformation, but they remain *in situ*. They do not form a many-layered epithelium after the ordinary pattern; they have rather a tendency to run out into a number of papillary processes. The reason of their accumulation *in situ* is probably, as has been already suggested, the fact that the excitation is not the progressive excitation of evolution, but a certain low degree of the functional activity called erroneously into play and acting at the same low rate for an indefinite time. The secretory product under these circumstances would appear to be a more stable product than are the waste cells produced by a corresponding functional stimulus in the healthy evolution, and no doubt the increment of the secretory force in the latter case accounts for the difference. The cell is, however, still a product of the secretion; its yellow colouring is conclusive on that point. It belongs to exactly the same category as the waste cells of the healthy process; and, to adopt the convenient formula that has been used already, those yellow cells are produced according to the law of endogenous cell-formation. Such products, again, have been explained to be "metaplastic" or heteroplastic.

The large yellow cells are not the most abundant constituents of the new growths in the bitch—in those of the human subject they do not appear to occur often—nor can any considerable part of the morbid structure be referred to transformations of them except in one or two cases; but they are found in almost all the tumours as an important concomitant of the other processes, and they have a special importance for investigation from their striking colour. They are in fact, as we found also in the physiological part, to be taken as representing the waste products in general; and the explanation of pathological processes in the breast becomes much easier and more objective if they are used, with due caution, in that capacity. Up to this point we have found that, in the spurious excitation of disease, the pigmented cells are produced in excess within the acini. But in most cases it is not inside the acini, but in the fibrillar tissue outside that they are found in greatest numbers. In Fig. 14, illustrating the normal evolution, there is seen a large collection of precisely the same cells in the tissue surrounding the secreting structure, and it has been explained that the large accumulation at one point was in that case the result of an accident. Now in the mammæ subject to a diseased process, such collections are constantly found. The cells are frequently deposited in several rows between the acini—which are themselves the seat of morbid changes to be described afterwards—but the largest collections of them are in the wide tracts of fibrillar tissue which separate the lobuli in the resting state, and which appear to become much more extensive in the mammæ of aged animals, just as the fibrous stroma of the breast becomes the predominant tissue in women at or beyond the climacteric period. In those tracts of fibrillar tissue the pigmented waste-cells are sometimes found in large irregular heaps; more frequently they are seen to be arranged in certain regular lines, which obviously correspond to the pre-existing lymphatic spaces. In such situations they usually lose their roundness; they become oblong, with their opposed ends flattened, and not unfrequently they become long, narrow, and fusiform. The nucleus, which is generally visible, takes on a corresponding alteration of shape. Fig. 25 is a high-power drawing of one small portion of a field that is quite covered with the large round yellow cells. It is from the diseased mamma

of a bitch, the same from which Fig. 22 is taken. The latter, from the less changed part of the gland, will serve to show pictorially where the yellow cells in the fibrillar tissue have come from; the pigmented cells of Fig. 25, which are disposed in groups in the fibrillar tissue and which contribute to the bulk of the tumour, are the same yellow cells that were before seen *in situ* in the acini of the gland. If the extra-acinous collection be examined closely, it will be seen to be made up of rows of

Fig. 25.

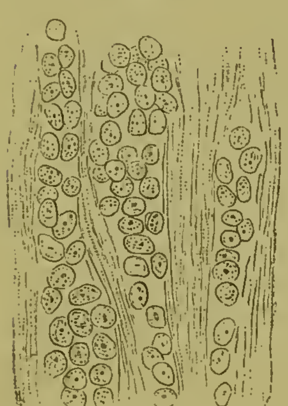
From a mammary tumour in the bitch. The fibrillar stroma of the mamma invaded by rows and alveolar groups of *large yellow granular cells.* Magnified 300 diameters.

cells which unite to form alveolar groups. Often a single file of cells extends for a long distance across the field; or there may be a double row, or any variety of grouping up to the alveolar collection, half a dozen cells or more in breadth at its broadest part. In the immediate neighbourhood of acini, or in the spaces between them, the arrangement of the yellow cells nearly always follows the circular outline of the acinus. It does not appear that the large granular pigmented cells ever undergo division of

their substance. If the collections of them increase in extent, it is by the addition of fresh supplies from the original source. But they are found to undergo certain transformations, and the derivatives of the pigmented cell, the cells resulting from such transformation, appear to multiply in the usual manner. The transformation consists most commonly in the loss of their pigmented cell substance.

In order to take advantage of the illustrations of extra-acinous grouping of cells, which are afforded by the waste cells of the pigmented stage, it is desirable to refer here to a very common type of tumour of the human female breast, although its component cells may seem to have an entirely different origin. Fig. 26 is a drawing of one of the most common appearances in the intensely hard skirrhus of the breast of women at or beyond the climacteric period. In this particular case the patient was fifty-eight years old. If the figure be compared with Fig. 25, the cells will be found to be very different; they are rather less than half the size, they are little else than nuclei without cell substance, and they have no pigmentation. Those differences are, however, unessential to the argument; they are merely the differences between one kind of epithelial waste product and another. The essential point of similarity is the presence of cells in the interfascicular spaces, and the grouping of the same. The position of the cells in the two cases is precisely alike. A certain number of them are arranged in single file, and these have frequently a cubical or discoid shape from the flattening of their opposed sides; the greater number of them are grouped in alveoli of varying breadth, and the alveoli are obviously made up by the fusion of two or more rows of cells. In short, if the preparations from the case of skirrhus of the human breast are compared with the preparations from many cases of tumours in the bitch, which have the pigmented cells as part of their constituents, the resemblance in the grouping of the cells is found to correspond throughout; and there arises the strongest presumption that the cells of the skirrhus

FIG. 26.



From a skirrhous tumour of the human female breast. The fibrillar stroma of the breast occupied by rows and alveolar groups of nuclear cells. Magnified 300 diameters.

are of the same origin and subject to the same influences as the pigmented cells, which are known beyond all doubt to be the waste products of a feeble degree of the secretory activity. The strong presumption that arises at this stage of the inquiry will be supported by a subsequent description of the same nuclear cells as actual derivatives of the epithelium, or as waste products of the secretion. In the meantime it is necessary to observe that the cells of skirrhus, although they are in great part situated outside the secreting structures of the gland, or the remnants of the same, are not all so situated; and further, that it is precisely in those breasts that have an enormous development of the interlobular fibrillar tissue, that is to say, in the breasts of women at or beyond the climacteric period, that the skirrhus form of tumour usually occurs.

The appearance drawn in Fig. 26 is selected, because it is almost exactly the same as that figured by Virchow to prove the origin of the cells in cancer of the breast from the pre-existing connective-tissue cells of the part[1]. The direct evidence in favour of Virchow's theory is necessarily inconclusive; the appearances are ambiguous, and the theory is hardly capable of proof by direct and objective demonstration. But Virchow's theory of the origin of the cells of cancer is only a corollary of one of the doctrines of the cellular pathology. Instead of the universal exudation or plastic lymph of the earlier school of pathologists, he finds that the all-pervading connective tissue, the cellular elements of which he himself demonstrated, is the matrix-tissue of new growths[2]. Virchow's substitution of the cellular elements of the connective tissue for the formative blastema or plastic lymph of his predecessors has long been an accepted doctrine, and the historical value of that great step in pathological knowledge will never be forgotten. But it has become more and more difficult, in view of the numerous contributions to general pathology made in the interval, to maintain Virchow's connective-tissue doctrine in its entirety. Even in so general disorders as secondary infections, whether acute, or chronic, or tumour-infections, it appears to be not so much the all-pervading connective tissue, as the predominant

[1] *Cellular-Pathologie*, p. 539, Fig. 146. See also the diagrams in Virchow's *Lectures on Tumours*, Lecture V.

[2] *Cellular-Pathologie*, p. 485.

cells of each particular region that take on the infected action, producing secondary abscess, tubercle, or tumour, as the case may be. Still less is it tenable that the connective tissue, all-pervading though it be, may form the matrix of all the primary new growths that have been referred to it. In so far as the tissues of the connective series are the matricular tissues of new growths, it is not from any general liability of that kind of tissue, but from a particular liability of the tissue in each particular region. Thus, if the stroma of the breast be really the source of the cells that go to make a skirrhous tumour, that is a local and special activity of the stroma of a particular gland. The stroma of the breast, according to my conclusion in the fourth chapter, is the same in its histogenesis as the glandular parts; and a systematic investigation of the climacteric changes in the breast may be expected to show something like an obliteration of the glandular parts as distinguished from the stroma, or at least a condition in which the stroma greatly predominated. It is in that condition of the breast that the skirrhous form of tumour is apt to occur. For that particular form of mammary tumour, therefore, the question of its histogenesis is not absolutely as between connective tissue stroma on the one hand and epithelial glandular structure on the other. Skirrhous cancer of the breast is a disease incidental to the effacement of the glandular structure, and to the absolute and final withdrawal of the secretory force. The real point at issue as regards Fig. 26 is whether the cells have developed where they lie, or whether they may be regarded as mobilised cells of the organ or of the remains of the organ; and the similarity of grouping in Fig. 25 affords a certain amount of evidence on the one side.

The theory of the epithelial origin of such tumours as skirrhus of the breast has often been objected to[1], inasmuch as that theory seems to afford no explanation of the heterology of the new growth. Such tumours have no doubt been described as formations of "atypical" epithelium[2], but it has not been explained wherein the atypical element lies. Besides the word "atypical," there is nothing in the statements of Waldeyer and other supporters of the theory, to show wherein the new growth differs from a mere hyperplasia; their language is merely the language of structural exten-

[1] Virchow, *loc. cit.* p. 569.

[2] Waldeyer, *Virchow's Archiv*, Vol. 55.

sion; the new growth depends upon "proliferation," "budding," &c. On the other hand, the atypical element or the element of heterology, in Virchow's theory, is explained by deriving the quasi-epithelium of the new growth from the connective-tissue cells. But the heterology of the tumour formation in a secreting organ is sufficiently explained according to an argument that I have already stated. The pathological activity of the breast is not merely in the way of structural growth; the functional factor is inseparably associated with the structural. The cellular products of the gland, whether under normal or morbid circumstances, are in the nature of things metaplastic; and if the cellular products of the gland, or the waste cells of the secretion, aggregate to form a tumour, that tumour is in the nature of things heterologous.

Returning from this digression to the illustration of morbid physiological action in the mamma of the bitch, and taking the phenomena in their physiological order, we come next to a certain class of pathological processes that play a far greater part in the actual formation of new growths than the simple but striking waste production of the pigmented sort which was last described. These also have their type in a certain phase of the normal activity of the breast. They correspond to a more advanced stage of evolution, or, absolutely, to a higher degree of functional excitation. It is necessary, however, to refer at this point to an elementary fact or law of tumour-formation in the breast, which underlies all the varieties of the process.

In nearly all the cases of mammary tumour-disease in the bitch, the fringes of gland tissue round the tumour, or the glands generally, where the whole of them could be examined, were found to be either in the extreme involuted condition or to show only the first removes from the resting state. The most probable inference from that fact is that the gland became subject to the morbid influence while its structure was upfolded and its function quiescent. The particular portions of the chain of glands where circumscribed tumours or more diffused enlargements are found, are those parts of the organ in which the morbid excitation has begun earlier, or has advanced more rapidly, or has in general met with more favourable conditions.

The various forms of tumours, as the sequel will endeavour to show, correspond to the various states of the secreting structure, and to the various degrees of the functional force, as measured on the physiological scale. Collections of the large pigmented cells, the earliest or lowest gland products, are generally found as concomitants of the tumour-formation, and in some cases those cells or their derivatives are a not unimportant part of the new growth; cells corresponding to a stronger degree of the functional force are the elements of tumour-formation in an important class of cases to be described immediately; and in the next chapter, varieties of mammary tumours in the bitch will be discussed, which appear beyond all doubt to correspond to that condition of the secreting structure and to that degree of the secretory force which, in the physiological chapters, was found to be associated with the production of mucus. It does not appear, however, that the degree of spurious excitation whereby these characteristic varieties of structure are produced, can be attained to by the gland without the earlier and lower degree of excitation, the first departure from the resting state, having preceded it. The breast is an organ that is made subject to periodicity; taking it at the resting state, it cannot under any circumstances reach the perfection of its function without going through the somewhat slow series of unfolding changes. When the evolution that is set up is of a spurious kind, or in other words, when a gland is disturbed from its resting state by some cause other than pregnancy, the steps of its unfolding are less orderly than in the normal evolution; and the fatality of the morbid process consists in this, that the spurious excitation never carries the gland to the end of its unfolding, or to the perfect degree of its function. The products of the gland never get beyond the crude condition, and it is the crude or cellular kind of secretory product that makes the tumour.

But although the facts themselves, as derived from the series of cases in the bitch, go to prove that the diseased excitation attacks the gland in the resting state, and leads it so far through a course of spurious evolution, it is not to be forgotten that there may be interferences with the activity of the gland at other times or under other circumstances. Thus, the characteristic disorder of the breast during lactation, or on a sudden stoppage of lactation,

is inflammation and abscess. Again, although it may not be possible to obtain precise clinical facts in evidence, it is reasonable to suppose that the upfolding process of the breast at the end of suckling may sometimes take a morbid direction, or the subsiding force continue as an enfeebled excitation for a length of time[1]. As regards the prolonged unfolding process during pregnancy, it is not difficult to imagine circumstances, such as abortion, which may cause the gland, or some part of it, to leave the

Fig. 27.

From the mamma of a cat pregnant with fœtuses 3½ inches long. Nuclear condition of the epithelial cells. Magnified 300 diameters.

beaten track of health. Tumour-formation may very well be incidental to the periodical upfoldings and unfoldings of the breast, but there is a want of positive evidence that it is so.

Premising, then, that most cases of tumour-formation in the bitch begin with those early evolutional changes that have been already described and figured (Figs. 21 to 25), we come at length to treat of actual new growths that have their structural type in a more unfolded condition of acini and in a higher degree of the

[1] In the case of a woman with cancer of the breast, who bore children up to the age of about forty-five, I elicited from her a fact that she had specially noticed, viz. that a fluid escaped from the breast for several months after the weaning of her last child.

secretory force. The type of their cells may be said briefly to be that condition of the normal glandular epithelium which is represented in Fig. 27, repeated from the second physiological chapter.

The figure gives the appearance of the mammary acini in the cat at the period of unfolding that follows the production of pigmented waste products, and that precedes the formation of mucus. The epithelium of the acinus at that intermediate stage is in the form of somewhat large and granular nuclear cells. Compared with the perfect epithelial cell, they are all nucleus and without cell-substance; compared with the nucleus alone of the perfect epithelial cell, they are larger and more granular. Without entering again into the question whether they themselves are thrown off from the acini as waste cells, they may at least be taken to be the crude kind of epithelium in which an imperfect secretory force resides.

Now, although the fact has not been sufficiently noticed by pathological writers and has certainly never been placed in its exact physiological category, the most ordinary cell in mammary tumours of the human subject is this same large nuclear cell. It has been the general practice hitherto to consider the healthy breast always as the fully expanded breast, and to take account of no other epithelium of the breast than the perfect polyhedric nucleated epithelial cells; and pathological writers who have described tumours of the breast as excessive and irregular growths of epithelium have either tacitly ignored the difference between the pathological cells and the polyhedric epithelium, or, having admitted a difference, they have treated the tumour cell (cancer cell) as one of those entities that exist for pathology alone, and in antagonism to health. But the somewhat large and granular nuclear cell of mammary tumours is nothing else than the crude epithelium of the middle period of evolution. There can be no doubt that the large yellow cells described and figured at the beginning of the chapter are the same yellow cells that occur at the earliest stage of the normal evolution of the breast; and there is just as little doubt as to the identity of the nuclear cells in the respective cases.

Fig. 28 is a drawing of one of several contiguous acini from a diseased mamma (mammary tumour) of the bitch; with reference

to the concluding statement of the last paragraph, the villous processes of cells in the figure may be at once compared with the villous outgrowths of pigmented cells in Figs. 23 and 24, and the exact similarity of grouping in two very different forms of cell cannot escape notice. In the adjoining figure, one side of the acinus, seen in profile, has the nuclear epithelium massed either in more layers than one, or in a number of villous or knob-like processes. The appearance is perfectly characteristic of the whole of that

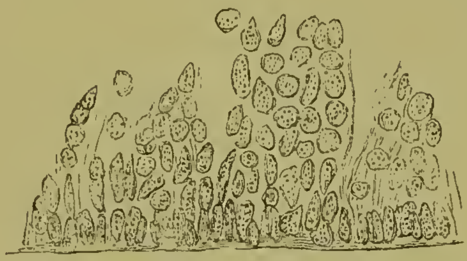
Fig. 28.

From a mammary tumour in the bitch. The epithelium of the acinus massed in several layers or in processes. Nuclear condition of the cells. Magnified 300 diameters.

particular case; and the process, with its modifications and developments, is one of the most common of the pathological processes within the breast that, in the gross, make up a cancerous tumour. Several other cases of tumour in the bitch, both the cases in the cat, and certain cases in the human subject, are directly referable to the same initial process. The acini are for the most part greatly enlarged, so much so in certain cases that the section of the tumour has to the naked eye a reticular appearance depending on their

prominent outlines. In those of them where the process is not complicated, the wall of the acinus, or the floor of it, is seen to be covered with a number of wart-like prominences; as many as ten or twelve of these may be seen arising from the floor of a single acinus. The prominences are for the most part simple aggregates of nuclear cells having a distinct nucleolus, and they are built up with some regularity so as to leave a small central lumen. The earlier stage of these prominences is seen to be a narrow solid column of cells; and such piles of cells are simply a modification of the many-layered condition of the lining cells of the acinus[1].

FIG. 29.



From a tumour of the human female breast. Portion of the wall of an enlarged acinus, showing the epithelium massed in several layers. Nuclear condition of the cells. Magnified 300 diameters.

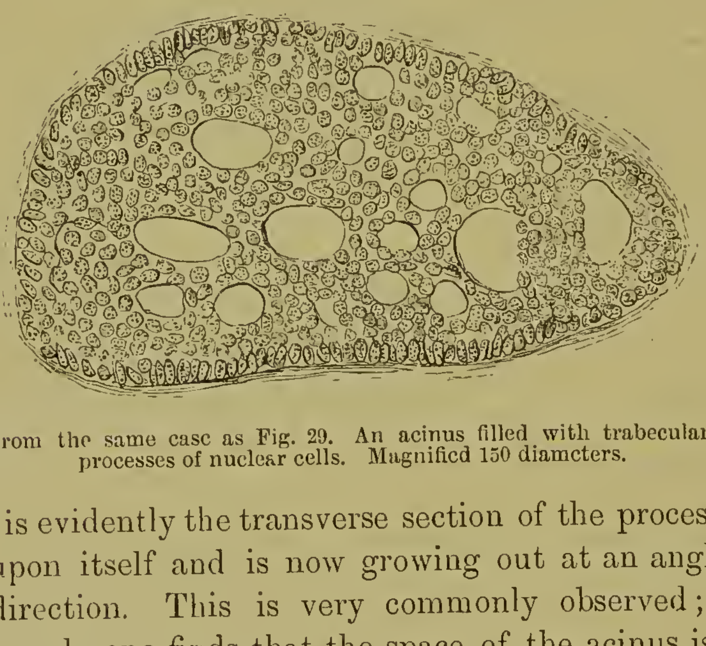
Fig. 29 is a drawing of a part of one side of an acinus from a mammary tumour in a woman. The entire tumour, which was situated at one side of the nipple, of small extent, well circumscribed and of somewhat soft consistence, was made up of nothing else but this condition of the acini and of the further developments and direct modifications of the same. The tumour is in fact representative of the intra-acinous class of new growths, which correspond most closely to the clinical division of medullary cancers

[1] As an opportunity will not be found to return to the point, one of the common developments of the intra-acinous papillary processes may be referred to in passing. The lumen that tends to form in the centre of the column of cells is often occupied by blood-vessels. The papillary process then acquires a sort of bi-pennate appearance, the line of the blood-vessels forming the raphe, and the epithelium being arranged regularly along each side of it. The vascularised processes often anastomose, in the way that will be afterwards described for trabecular structures within the acini, and there results a network of columns having an epithelial covering on each side, the original outlines of the acini being in the end obscured. When the vascularised papillary processes do not anastomose, they project into the acini as if they were imperfect septa. Langhans (*Virchow's Archiv*, Vol. 58) has described the same appearance, but he attributes it to an actual breaking down of the septum between two acini, as in emphysema of the lung

of the breast. The figure shows an appearance very much like that of an epithelium of many layers. The lowest layer appears of a deeper colour, being made up of the more cylindrical and pyramidal forms of cells closely packed together; and that is precisely the character of the lowest layer of a normal epithelium of several layers, as, for example, that of the trachea. The upper cells are rounder and separated by a larger amount of intercellular substance, and the free border may be seen to run out into processes of the same kind as those referred to in the preceding figure. All the cells that line the walls of these acini, and in some cases occupy the entire space of the acinus, are of the nuclear kind.

It may be observed that the columnar processes of the large yellow cells, such as are figured on p. 131, showed a tendency to bend over at their free ends. The same may be observed in Fig. 28. The round disc-like appearance in the upper of the two

Fig. 30.

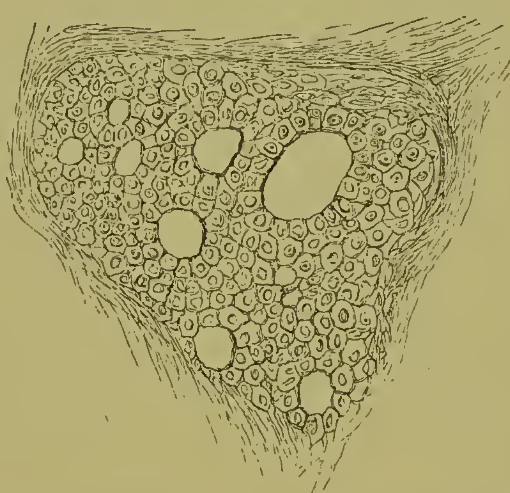


From the same case as Fig. 29. An acinus filled with trabecular processes of nuclear cells. Magnified 150 diameters.

processes, is evidently the transverse section of the process that has doubled upon itself and is now growing out at an angle with its original direction. This is very commonly observed; and still more commonly one finds that the space of the acinus is occupied in all directions by trabecular columns of cells, which are nothing else than the processes that have become fused together at their free extremities. Fig. 30 is a drawing of an acinus from the case that Fig. 29 has been taken from. The entire space of the acinus, it will be observed, is occupied by anastomosing columns or trabeculæ of cells; the cells are all of the same nuclear kind, with a certain amount of intercellular substance. The subjoined figure

No. 31 has a great resemblance to the preceding, but it shows differences in the character of the component cells that are not without significance. Fig. 31 is from a tumour of the human male breast. The patient, a man past middle age, had a tumour in each breast, one of them quite small and firm, the other larger and in parts softened. The drawing is taken from a firm and undegenerated part, and represents the prevalent structure. The growth consisted of greatly enlarged acini, sometimes packed closely together, but in general with a certain amount of coarse fibrous or chronic-inflammation tissue between them. Within the acini, the epithelium was of a perfect polyhedric type, consisting of

FIG. 31.



From a tumour of the human male breast. An acinus filled with trabecular columns of polyhedric nucleated epithelium. Magnified 150 diameters.

nucleated cells with a broad fringe of almost hyaline protoplasm. There was everywhere a considerable hyperplasia of the epithelial cells, which sometimes gave the floor of an acinus a ridged appearance, but more often resulted in the trabecular filling up of the free space of the acinus, as shown in the figure. In some situations the cells were more elongated or lozenge-shaped, but there was everywhere the same relation between the central nucleus and the investing cell-substance. When the cells were seen edgewise they appeared to be thin plates, resembling squamous epithelium. The only other point that requires to be mentioned by way of description is, that the softening or degeneration of one of the tumours consisted in the caseation of large numbers of the detached epithelial

cells within the acini. The appearance of the softened parts to the naked eye was caseous, and with the microscope the acini were seen to be filled with heaps of rounded cells, which had the usual blurred outlines and opaque substance of cells that had become caseous.

The significance of the form of the cells in this case lies in the fact that it was a tumour of the male breast. The male breast, although it developes for a time like the breast in the female, soon loses the capacity of functional excitation with which it was originally endowed; while something of its structure remains. There is, as it were, a severance of function from structure. But the structure is still capable of excitation; it may be subject to irritant influences like any other part of the body. The effect of the excitation, in whatever way the latter operated, is seen to be a purely hyperplastic effect. The new growth of epithelium is polyhedric nucleated epithelium, and not the crude products of a feeble secretory stimulus. Again, the transformation of this epithelium is not any of the transformations of secreting epithelium, for instance into a mucous or a fatty substance, but it is a *caseous transformation*[1].

Continuing the comparison between the two figures No. 30 and No. 31, in the latter the hyperplastic process can be seen by itself; if it is succeeded by another process in the individual cells, that process is one of caseous degeneration. But in the diseased acinus of the female breast, the hyperplastic or formative process and the functional or transforming process are both implicitly present in one and the same act. In tumours of the female breast the perfect polyhedric kind of epithelium is seldom found; the kind of cell that is most commonly found both in skirrhous and medullary cancers is the large nuclear cell. Measured on the physiological

[1] Caseous transformation of hyperplastic epithelium occurs elsewhere in the body, very commonly in the epithelium of the lung alveoli and in the cells of the suprarenal body, and it cannot escape notice that the cells in both of those situations are epithelial-like cells in exactly the same position as the epithelial cells of the male breast; that is to say, they agree in being not subject to the ordinary functional excitations of glandular epithelium, and they have a considerable morphological resemblance. It may perhaps turn out to be a sound generalisation, that the caseous transformation of hyperplastic epithelium befalls only those epithelial cells which are capable of no secretory excitation.

scale, those cells belong to the intermediate stage of the breast's unfolding, and they stand for a half-roused functional stimulus. Although, in the cases from the bitch, there is good evidence that a still feebler stimulus, bringing the function up from the resting state, must have gone before, it is at the later or intermediate stage that the pause in evolution is made, and it is at that level that the continuous morbid action of the gland proceeds for an indefinite time.

The effect of the continuous action of a feeble secretory force is well seen in the Figures 28 to 30. Under ordinary circumstances, the product that is formed within the acini, however crude it may be, leaves the gland. There is abundant evidence that, in the normal evolution, large numbers of the most imperfect secretory products, viz. the pigmented cells, leave the gland by the lymphatic channels or otherwise. Under the spurious evolutional influence, they follow the same inherent tendency so far. But it is not uncommon to find accumulations of them *in situ*, as shown in the Figures 23 and 24. Although the morbid excitation corresponds in its intensity to a stage of the normal evolution, there is this fundamental difference, that the corresponding stage of the normal process is transient, giving place to a stronger force, while the morbid process continues indefinitely at the same enfeebled level. The discharging force of the gland is therefore weakened, inasmuch as the increment of the function is necessary to its vigour. Elements that are really secretory products of the gland tend to accumulate within the acini, and the process takes on the aspect of a purely formative or proliferative process. Nothing could be more suggestive of proliferation than the almost vegetative growth of pigmented cells in Fig. 23; but nothing is more certain, at the same time, than the functional significance of the cells. They are themselves the crude secretion, and they differ from their physiological prototypes only in accumulating within the secreting structure. If the cells had less obvious marks of functional transformation upon them, it might be said that the distinction insisted upon between formative and functional action is a merely theoretical distinction and without existence in fact. But the characteristic pigmentation is an evidence that the cells do not result from a formative impulse only; it is evidence that the dualism of function and structure is undissolved even in disease.

The case of the tumour of the male breast affords a convenient illustrative contrast. In the male breast the function falls into disuse at an early period, but something of the structure survives; the union of structure and function is as it were dissolved. Consequently, the result of a morbid excitation might be expected to be mere hyperplasia; and so indeed it is in this case. The form of the epithelium indicates hyperplasia alone; and the only change that it undergoes is in the way of caseous degeneration.

The cells that fill the acini in Figs. 28—30 are therefore not only the epithelium of the acini, but they are at the same time the crude products of the secretion. The formative process no doubt outruns the functional, and that must be held to be one of the most important points in the causation of the tumours. The cell that should have passed out of the gland as a waste cell, remains in the place of its origin and begins to multiply there. The work of proliferation may be seen in Fig. 29. In the deepest layer of cells, some of them are found to be elongated, with a nucleolus at each end; appearances of constriction in the middle may be also observed, and the division of the cell into two may be at once inferred. The cell that should have been thrown off from the acinus almost as soon as it was formed, remains, with its progeny, to infest the glandular structure. Such cellular products of the function are inevitable in the breast, owing to its periodicity; the initial error consists in the gland being disturbed from its resting state by some unusual cause; and the misfortune lies in the indefinitely prolonged formation of crude cellular secretion, without any approach to a higher and safer intensity of function, and in the retention within the gland of the crude secretion, either as intra-acinous accumulations, or as extrà-acinous infiltrations. It is upon such deviations from the physiological track that the existence of a tumour depends. So far as relates to the large nuclear cells, the intra-acinous collections of them correspond to the structure of medullary cancer, and the extra-acinous infiltrations of the same cells are a distinguishing feature of skirrhus.

CHAPTER VII.

PATHOLOGICAL PROCESSES OF THE BREAST—*continued.*

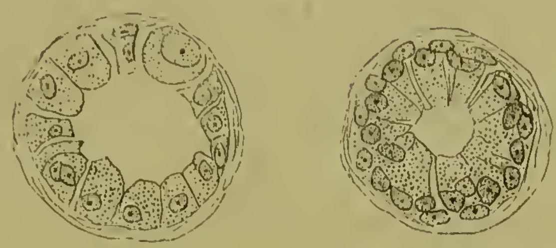
In attempting to refer to their physiological type the pathological processes last discussed, I was under the disadvantage of having for the normal standard a period of the evolution of the breast that is itself difficult to explain. I pointed out in the second chapter that the earliest evolutional changes in the breast could be followed without difficulty, owing to the pigmentation of the cellular products that characterise them; and that the latest changes were intelligible, inasmuch as the vacuolated cells within the acini differed from the colostrum or milk-containing cells only in the circumstance that their vacuoles were filled with mucus. The large yellow granular cells are products of the secretion so well marked in every way that their occurrence, both in healthy and in morbid states, may be safely taken to support even the novel pathological doctrine that has been stated. Hardly less reliable in the pathological application are the phenomena of the breast in the immature period which is characterised by the production of mucus. A considerable proportion of the tumour cases in the bitch have their physiological type in that condition of the organ and in that intensity of the function. The physiological type is that of the later period of the evolution, in which the function comes near in its intensity to the perfect lactation. But there is every reason to think that the morbid process, even when its prevalent characters are those of advanced evolution, has started from a resting condition of the breast, and has advanced in the usual way through the earlier stages to the later. In the tumour

cases about to be described, the glandular tissue round the centres of disease is for the most part in the resting state, and, in the more diffused morbid enlargements of the gland, or in the younger tumour nodules, one may find undoubted traces of the earlier stages of evolution. In no other varieties of the tumour disease are the pigmented cells so numerous, although the actual tumour has often the myxomatous or cartilaginous character.

However far the spurious stimulation of disease may carry the mamma from the resting state towards its perfect evolution and its perfect secretory activity, the stages of the diseased process are always more tardy than in the evolution of pregnancy, and the pathological investigation often affords an opportunity of detecting some particular state of the mammary epithelium, which in the normal study was rather a matter of logical proof than of actual observation. Thus, in a diseased mamma, the pigmented granular condition may be observed in the complete set of cells within an acinus, while in the evolution of health seldom more than two or three pigmented cells are seen *in situ*, although they may be numerous outside the secreting structures. The well-marked stage of mucus production that occurs in the latter half of evolution may be also more deliberately observed in the spurious excitation of disease. The gland or some part of it becomes for the time being a mucous gland. Fig. 32 shows two mammary acini which are taken from different cases in the bitch. It would be difficult to obtain from any part of the digestive tract more perfect examples of mucus-producing structures. Although there is abundant evidence that, in the healthy mamma, a certain incomplete degree of the functional excitation both in involution and in evolution has for its effect the production of mucus from the secreting cells, the cells are not to be found ever at that point of their existence when they have the characters of perfect untransformed mucous cells. Those characters are, a somewhat columnar shape, the nucleus placed towards the attached border of the cell, and a large amount of cell-substance which has the peculiar and, as it were, succulent aspect found in secreting cells belonging to that class. In the corresponding stage of the evolution of pregnancy, the cells are found to be all of them vacuolated more or less extensively, as in Fig. 17; the condition of the gland is probably analogous to those states of the intestinal

mucous membrane, or parts of it, where the epithelial cells are found in the condition of goblet cells. Why the production of

FIG. 32.



Mammary acini, from two different pathological cases in the bitch. The epithelium in the form of perfect mucus-producing columnar cells. Magnified 300 diameters.

mucus from the epithelium of the mamma should coincide with a subsiding or an incomplete degree of its functional force is not at all clear; but it is a well-established fact that the mucous transformation of the mammary cells occurs at exactly corresponding periods in the parallel processes of involution and evolution, and it may be taken absolutely to be the characteristic effect of a limited functional excitation. Corresponding to this degree of the secretory force there is a group of pathological processes in the mamma which are of frequent occurrence, and which are the point of departure for many of the tumours in the bitch and for some of the varieties of mammary cancer in the human subject. Such tumours often correspond closely to the cystic sarcomas, or myxomas, or colloid cancers; but as we have been led, for sufficient reasons, to avoid treating the tumours according to their classes, the names are mentioned here solely to show what are the familiar tumours that now fall to be discussed.

The mucous-gland structure of Fig. 32 is perfect of its kind, but it is itself rare in the mamma, and is found more commonly in certain states of transformation. Enlarged acini occur in which the cells, forming a circlet round the wall, are spherical and distended with mucus-like protoplasm, or actually vacuolated like the cells in Fig. 8 on page 18. The cavities of acini are not unfrequently seen to be filled with the same large vacuolated cells. The distinction between them and the colostrum cells proper is in their substance only; the form is the same, but the substance, in the one, takes on the degree of staining characteristic of mucus or of mucus-yielding protoplasm, while in the other it remains mostly unstained and of a greyish appearance.

In some acini, the cells on their wall are the yellow cells of the earliest evolutional stage, and there are transitional cases where the pigmentation is fainter, while there is the same vacuolated condition of the protoplasm as in the actual mucous cells.

These are the acini in which there is the smallest extent of deviation from the normal. The transformations of the epithelium that have the most direct relation to the tumour process are somewhat different. For one of these varieties a brief description must suffice. The acini are filled with large collections of mucus penetrated with vesicles in all directions, and in this mucus lie a number of round deeply-coloured nuclei. In favourable specimens, the vesiculated mass of mucus is seen to be an aggregate of many vacuolated cells which have the round nuclei in their cavity or on their periphery. As to the cells that line the wall of the acini in those cases, they are also nothing but deeply-stained round nuclei, with no obvious cell-substance. Two cases of tumour in the bitch, one of which had a superficial cyst and was highly malignant (the liver being full of secondary tumours), were made up chiefly of groups of acini containing cells of the above category. Generally speaking, the acini were grouped in the ordinary lobular arrangement; so far, the change in the gland occurred uniformly throughout its substance. The interlobular tissue was extensive, juicy, and often filled with numbers of the large yellow and other cells. Inside the acini the cells were either in more layers than one, or they ran out into processes, or they completely filled up the acinous space. In these points the pathological process resembled that already described for two other varieties of waste products, the large yellow cells, and the kind of cells in Fig. 28 and Fig. 29; the intra-acinous papillary processes seemed to begin with a submucous collection of the nuclear cells, which had the effect of raising the surface-cells. The chief difference lies in the fact that the cells now under notice are smaller and rounder, or more perfectly nuclear. Where the vacuolation process is obvious, they are the correlated cellular product of a more complete vacuolation. Where the vacuolation is not so obvious, they correspond to the waste cells where the functional excitation is considerable, and they have the closest resemblance to those drawn in Fig. 9, and in Figs. 5 and 6.

The normal mamma (of involution), from which the two last

are taken, shows other cellular products of vacuolation besides the small round cells. These are the crescentic, or rhombic, or triangular, or rod-shaped cellular bodies, which are derived from the vacuolation of cells in a perfectly intelligible manner. The same varieties of shape are found among the cells within the acini in the pathological states of the mamma that correspond to the mucus-producing period. In particular, the greater part of the tumour in another of the cases in the bitch consists of alveolar groups of these cells, and the alveolar arrangement is clearly enough seen to correspond with the earlier acinous arrangement. The cells, while retaining their various shapes, have very generally a narrow fringe of protoplasm round the deeply-coloured nucleus. This tumour might be considered a myxoma.

There is, however, among the cases collected, one in particular which illustrates so many of the pathological processes at once, that it may be selected for a more detailed and circumstantial description. The animal was an old setter bitch. In July 1873, a tumour was removed from one part of the mammary chain, globular in shape and lobulated, about two inches in diameter, firm in consistence and yielding on section a clear yellowish or brownish juice. There was one very small point of cartilaginous tissue near its centre. This tumour belonged to a variety that will fall to be described afterwards, among the concluding illustrations of pathological processes. In June 1875 the animal was brought back for treatment, the disease having re-appeared. There was now a large soft tumour towards the inguinal end of the other mammary chain, and there were several smaller nodules throughout the whole length of the mammæ on both sides, besides a more diffused enlargement about the middle of the gland on one side. The animal was considered to be past surgical treatment and was killed. The liver contained a number of small rudimentary nodules, and in the mediastinum there was an enormous lobulated mass of medullary consistence. At a point in the vena cava inferior about two inches below its termination in the auricle there was an oval mass of the same consistence, rather smaller than a hen's egg; it appeared to be connected with the tumour-mass in the mediastinum.

Some of the small mammary nodules were cartilaginous; others did not differ in gross characters from the gland-tissue that

surrounded them except in being circumscribed and of greater density or closeness of texture. The diffused enlargement, again, which extended over two inches of the mammary chain, obviously owed its special character to some process going on more or less uniformly throughout the gland over that area. To take advantage of the evident richness of this material, several sets of sections were made from different portions of it. Many parts of the mammary chain of glands were found to show the perfectly typical resting state. Another common appearance was that of acini in the first evolution stage, with large yellow cells within and around them. Some of the smaller nodules were made up in part of collections of the pigmented cells in the fibrillar tissue. Sometimes an entire lobulus is encountered, the acini of which have the mosaic of perfect epithelium as in the fully expanded gland. The epithelial cells, however, have unusually large and oblong nuclei, as shown in the right-hand group of cells in Fig. 2 drawn from another case. But the processes most characteristic of the case belong to the stage of mucus production. One of the acini of Fig. 31, showing perfect mucous cells, is taken from this case. Other acini, again, have a circlet of spherical mucous cells, or the same vacuolated; and there are to be seen in reality those gradations in tint between the distended spherical mucous cells and the large yellow cells of an earlier stage, which, in the study of the physiological evolution, are rather an inference than a matter of observation.

But the most instructive appearance of cells within the acini is that drawn in Fig. 33. The figure contains two adjoining acini, the upper of which is incomplete, but shows very well the cells individually. The lower is a complete acinus with two apparent diverticula, which are no doubt the infundibula of adjacent acini that have been included in the same plane of section. The acinus, it will be seen, has a small free space in the centre, and several layers of cells on its wall. This is the same pathological process that we have had to consider before, and as in the former cases, except in that of the male breast, the many-layered epithelium implies more than a mere hyperplasia. In the cancer of the male breast the cells were perfect epithelial cells, but in the other cases of hyperplastic acini, as in this, the cells are of another type. In Fig. 29, from a soft cancer of the female breast, the lowest layers

are oblong nuclear cells, while the upper cells are rounder. In the present case, there is the same admixture of elongated nuclear and other cells. In both cases the form of the cells is owing to the fact that there is not merely a hyperplastic process going on, but a functional process as well; there is in fact the dual activity of the secreting gland. In the present case, the activity corresponds to that degree of excitation which produces mucus from the epithelium. One acinus from this case has been figured already in which the epithelium has the perfect mucous type, and the same kind of cylindrical cell with the nucleus at its base may be seen in the half acinus at the top of Fig. 33. The obvious and unmis-

Fig. 33.

Mammary acini of the bitch (pathological). The epithelium massed in several layers; the cells columnar and nucleated, or spindle-shaped. Magnified 300 diameters.

takeable secretory change in the cell is where it becomes globular and vacuolates, and we have frequently had occasion to notice, both in the healthy processes and in the morbid, that the vacuolation may be associated with the production of a waste cell. But, where we find the formative excitation outrunning the functional, and the cells produced relatively so fast that they accumulate in papillary processes or in more layers than one, the secretory change is not so obvious. It is shown only in the altered shape and proportions of the cell. In all such cases of hyperplasia

belonging to the stage or degree of mucus production, the secreting cell tends to become an oblong, staff-shaped, or spindle-shaped cell. Among these pathological processes in the mamma, a whole lobulus is sometimes found in which the acini are lined with long, narrow, staff-shaped nuclear bodies[1]. In the figure now being described, it will be seen that they are mostly spindle-shaped. In the lowest layer a large pyramid cell occurs, with three nuclei.

The accumulations of epithelium within such acini as are represented in the last figure stand for more than a mere hyperplasia; the transforming or functional force is also present, and its effect is shown in the forms of the cells. But the presence of the functional factor is also shown in a much less doubtful manner. As the yellow cells of an earlier stage could be seen, both in normal and morbid cases, not only within the acini but also in the interacinous and interlobular tissue and ultimately in the lymph sinuses of the lymphatic glands; so the mucus-yielding epithelial cells of the present stage may be seen, in one and the same preparation, occupying the position of epithelial cells, and collected in heaps in the interacinous and interlobular tissue. Reverting to Fig. 32, in which the mucus-yielding cells are of a somewhat cubical or columnar shape, cells of precisely the same form and substance are found in rows just outside the acini. Were it not for the analogy of the large yellow cells, whose escape from the acini into the neighbouring tissue cannot be questioned, the occurrence of large cubical epithelial cells outside the acini might appear to depend on some error of interpretation. It might, for example, be urged that the groups of cells that appeared to be extra-acinous were merely the contents of acini whose walls had given way in the section. But it is not more surprising that the mucus-yielding cells should leave the acini bodily, than that the pigmented cells of the more immature type should do the same. In the same preparations there are often to be seen circular belts of the yellow cells occupying the interacinous tissue, and near them similar interacinous accumulations of non-pigmented cells, sometimes of the smaller nuclear type, but not unfrequently of the more characteristic mucous type. The most common form of the latter is not the cubical or cylindrical cell, but a spindle-shaped

[1] An appearance of this kind is figured by Langhans, *Virchow's Archiv*, Vol. 58, Plate 3, Fig. 4.

cell of the kind that occurs most numerously in Fig. 33. The difficulty that one has to contend against here, one may say the incubus that has here to be shaken off, is the theory of the connective-tissue origin of all such cells. But two facts are established: first, that crude forms of epithelium do escape from the acini into the surrounding connective tissue, and second, that one of the forms of the crude epithelial cells is the spindle-shaped cell (Fig. 33). However apt, therefore, one may be to take the extra-acinous collections of spindle cells for products of the connective tissue in which they are found, that simple and conventional explanation must give way to one that is more in accordance with the facts. Cells of the oblong or spindle form are found as a somewhat morbid type of epithelium, and it is nothing more than their destiny, according to the normal scheme of the function, that they should leave the acini.

In the particular case which has been chosen to illustrate this variety of the tumour disease, the collections of fusiform or oblong cells outside the acini are very numerous. In the part of the glandular chain where the process is more uniformly diffused, they occur side by side with the other kinds of waste products. The smaller tumour nodules are in great part made up of aggregates of the elongated and spindle-shaped cells between the acini; it is their presence or their retention there that changes the glandular structure at various points into a corresponding number of small tumours. The more extensive the interacinous collections of waste cells are, the more do the outlines of the acini become obscured. In this manner the structure of the diseased breast comes to be that of an "adeno-sarcoma," the sarcomatous element being represented by the spindle or other cells outside the secreting structure, and the adenomatous element by the same kind of epithelial cells that are still *in situ*. Some of the less cystic varieties of "cystic sarcoma" correspond to the same morbid condition of the breast.

The particular case that has been so far described contained one very large tumour and a number of smaller nodules. It now remains to give an account of the former, and the explanation of the smaller nodules will be found to lead up to the theory of the principal growth. The large tumour occurred towards the inguinal end of one of the glands; it was globular in shape, about three

inches in diameter, of uniform soft consistence and whitish colour. Fig. 34 represents the minute structure as it appeared in sections taken from a central and representative part of the mass. The predominant cells are oblong or fusiform, and of granular substance. In every part of the section there is seen a certain arrangement of the cells which is not sufficiently conveyed by the figure. The tracts of oblong or fusiform cells follow a sort of figure-of-eight course; they enclose somewhat lighter or more empty spaces among them

FIG. 34

From a mammary tumour in the bitch. Broad tracts of oblong cells enclosing alveolar spaces which contain other forms of cells and mucus. Magnified 300 diameters.

at regular intervals. The lighter spaces are occupied by rounder and often larger cells, and by intercellular substance of a mucous nature. The tumour, as an entity or individual, might be classed among the myxo-sarcomata; but, according to the rationalistic interpretation of its growth, it represents a condition of the structure of the breast in which the extra-acinous collections of cells have encroached so much upon the acini as almost to obliterate them. The lighter alveolar spaces that occur at regular intervals throughout the section are the original acinous cavities,

occupied by a more spherical variety of cells and by mucus. The structure is a more extreme form of the extra-acinous retention of waste epithelial products that may be seen, in all stages and degrees, in the other and earlier centres of morbid action in the same mamma. In the largest tumour there is no doubt evidence of rapid multiplication of the oblong and fusiform cells in their extra-acinous situation; but there is no evidence whatever that the proliferating cells were derived originally from the connective-tissue corpuscles of the stroma of the organ. I am well aware that this account of the origin of the tumour is in direct opposition to an opinion that is universally held. But I submit, at the same time, that it so differs because it takes into consideration a factor in tumour-formation that is all but universally ignored, namely, the physiological or functional factor. Whether in health or in disease, there is an indissoluble union between the mammary structure and the mammary function, and that dualism is nowhere more apparent than in those immature periods of the breast which precede the perfect lactation. If the entire range of processes in the breast be set up as the physiological standard, such tumours as the one last described will not only seem to be the natural outcome of functional irregularity, but, on the other hand, the constantly assumed activity of the connective-tissue stroma will appear, in the light of that physiological knowledge, to be arbitrary as an assumption, and insufficient as an explanation.

The concluding illustrations of morbid processes, that are furnished by the series of cases from the bitch, relate to tumours in which there is a tendency to the formation of a kind of tissue that is cartilaginous in its hardness and sometimes resembles hyaline cartilage in its minute structure. The cartilaginous tissue in the breast appears in no case to develope as cartilage from the outset; it is always a cartilaginous transformation of some earlier condition of tissue, and generally of myxomatous tissue. The gristly character of the tissue depends upon a large amount of intercellular substance, which has become hard and firm like the intercellular substance of hyaline cartilage. The cartilaginous transformation is very apt to occur in mammary tumours of the bitch, and it is more often seen at limited points of the tumour than as a uniform change of its whole substance. A case occurred of an extensive tumour in the bitch, which was mainly soft

and succulent, but at certain places hard or gristly, and, at one central spot, truly cartilaginous and even calcified. There were numerous secondary tumours in the lungs, which reproduced the structure of the soft and succulent parts in the primary tumour. There is every reason to think that the cartilaginous transformation is a safe and, as it were, cicatricial issue of the tumour process, and that the infectiveness of the tumour diminishes in proportion as the sclerosis of its substance spreads[1].

In approaching the consideration of tumours of the breast that contain cartilage, or that are on the way to become cartilage wholly or partially, it might appear as if the physiological method, which has been sedulously followed in the preceding sections of the pathological investigation, must at length be given up. Is it conceivable that the epithelial structure and the secretory force of the breast should be in any way concerned in the production of a cartilaginous tissue? That, however, will be the conclusion drawn from the following descriptions and illustrations; and as the conclusion is an unusual one, I must premise that the subject is introduced here not for the sake of putting forward quixotic theories, but simply in order to complete the series of morbid changes which this collection of mammary tumours exemplifies. If it be personally a more agreeable task to substantiate the current opinions, it would no doubt also be prudent in the present case to abstain from adding still further to the unaccredited pathological doctrines that I have been endeavouring to expound and to establish. The cartilaginous forms of tumours might be disposed of, in a sentence, as growths of the connective tissue, and as unconcerned, therefore, in the physiological processes of the gland. But a prolonged study of mammary tumours in the bitch will satisfy anyone that there is no line of separation between the cartilaginous and the other forms of tumours. The assumption of their origin from the connective tissue of the gland might be easily made, and would be readily admitted. But such an assumption would be dictated by indolence, and I shall now endeavour to show that it would be based on error.

[1] The ordinary tumours of the parotid, partly myxomatous and partly cartilaginous, have a general resemblance to the mammary tumours in the bitch, referred to in the text. The parotid tumours are known to be comparatively innocent growths, which may have existed for many years without infecting the system.

Fig. 35 is a drawing of several contiguous acini from a case that had the cartilaginous tendency in a very marked degree. The large principal tumour was partly cartilaginous as well as partly osseous, and the smaller nodules exemplified other processes as well. The fringes of the more or less normal mamma showed exquisitely the process of pigment-cell formation in the acini,

Fig. 35.

From a mammary tumour in the bitch. A group of four acini, showing various changes of the epithelium. Magnified 240 diameters.

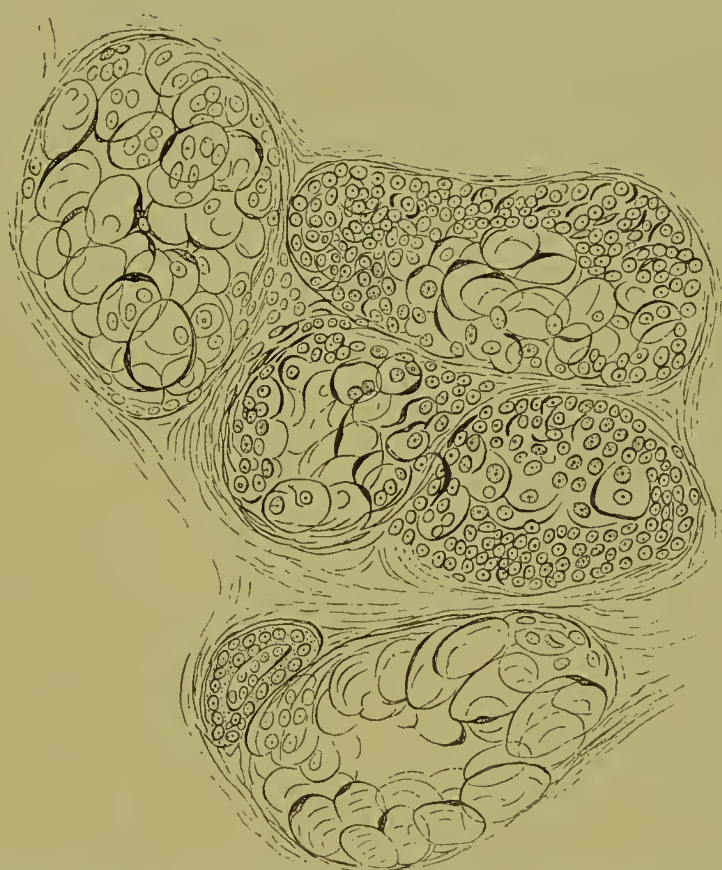
and many parts of the tumours had immense numbers of the large yellow cells in the fibrillar tissue. But the pathological processes, as a whole, have their type in another part of the physiological scheme. One of the acini in the figure will be found to have a trabecular growth within it not unlike those already described and figured; another shows a papillary process; while the whole of them show an unusual condition of their epithelial lining. The marginal row of cells are round nuclei of

considerable size embedded in some intercellular substance. In that respect the condition is the same as in the other cases of many-layered hyperplastic acini. But the condition in the lower layers is somewhat special, and it is in the differences exemplified there that the distinctive characters of this cartilaginous process consist. That difference may be said in a word to be the more real vacuolation of the cells, corresponding to a greater intensity of the functional stimulus.

In treating of the pathological processes to which the tumour of Figs. 32—34 is to be referred, it was mentioned that the perfect mucous cells were elongated cylinders, that an entire lobulus was sometimes found in which the epithelium was in the form of long narrow rod-shaped cells, and that the elongated or spindle form of the epithelium was especially well marked where there were more layers than one. The perfect mucous cells, as drawn in the pair of acini already mentioned, had a nucleus at their attached end and a large amount of granular cell-substance, but the cells of the pathological acinus were filiform or rod-shaped, or spindle-shaped. That circumstance was taken to indicate that the cells had undergone a certain degree of functional transformation; that they were not perfect epithelial cells, but in reality crude agents or products of the secretion. Whatever secretion proper they had given origin to was in the form of intercellular substance, but otherwise it might be said that the whole epithelial cell became waste. Now, the position that has to be advanced at this point of the investigation is, that a very common class of slender rod-shaped or crescentic bodies found in the particular pathological processes at present under review, are phenomena of the same class. The acini in Fig. 35 show several of these. In many cases the deeply-coloured crescentic line evidently corresponds to one side of a cell or of a nucleus; it represents in fact the peripheral solid part of a cell undergoing some kind of vacuolar transformation. The peculiarity of the pathological process is that the vacuolation does not result in the production of an actual fluid which is discharged, but of a *hyaline intercellular substance*, among which the deeply-coloured straight or curved bodies, as well as paler round nuclei lie. This account of the process will become much more intelligible and will doubtless gain in credibility by a reference to Fig. 36, which is taken from the same case as the

preceding. The acini contain a number of large cells resembling fat-cells. But the appearance in the preparation, although the woodcut may fail to give it so completely, is not that of cells filled with fluid, but of cells filled with a firm hyaline substance. The cells are in fact the vacuolated epithelium; the hyaline substance corresponds to the contents of vacuoles, and the crescentic or rib-shaped bodies to the peripheral masses. The figure

Fig. 36.



From the same case of mammary tumour as Fig. 35. A group of acini distinguished by their hyaline appearance. Extensive vacuolation of the epithelial cells: hyaline contents of the vacuoles. Magnified 240 diameters.

might be matched with another almost similar from a different case, and in the latter there may be seen in the immediate neighbourhood of the hyaline-looking acini, an acinus in which the cells round the wall have the ordinary appearance of vacuolated cells, with peripheral nuclei of considerable size. It is quite exceptional, however, to find the thin crescent-shaped or fibre-like bodies in their original relation to a vacuolated cell, and there is reason to think that the functional change to which they

are due is often not an obvious vacuolation at all. They are generally found scattered among round nuclear cells and in a hyaline matrix. Isolated in this manner, they are apt to be mistaken for the fibres of the connective-tissue framework in which epithelial cells are supposed to be set. But besides their relation to vacuolated cells, there is another position in which they are found that may clear up any doubts as to their real nature. One of the acini in Fig. 35 shows a trabecular band stretching across it, and the appearance is not uncommon in this and other cases. Sometimes the trabecules are much narrower than that in the figure; the free space of the acinus is bridged over by a sort of network. These trabeculæ at once suggest the epithelial trabeculæ already described in two cases of cancer of the human subject. In the present case they are made up of long rod-shaped cells and a quantity of hyaline intercellular substance; the principal difference between them and the trabeculæ of the other cases is that their cells are longer, narrower, and almost like fibres; but that is a difference that is quite in keeping with the altered circumstances of the case.

The two illustrations last introduced have the great advantage as regards brevity and directness, in that they show the pathological process within acini that are simply enlarged; the new growth so far depends on collections of cells in the lumen of acini, on several layers of cells round the wall, or on trabecular bands stretching across or filling up the space. But although the peculiar transformation of the individual cells is everywhere the same, that change in the cell is not, as a rule, associated with mere enlargement of the acini. Perhaps the most characteristic feature of these tumours is the growth in the acini (and in the ducts as well) of papillary and bud-like processes, which sometimes reach an enormous size. The bud-like growths are attached to the wall of the acinus by a short pedicle; the expansion of the process is globular, and sometimes its free extremity bends over, and, as it were, grows downwards again. The dilatation of a single acinus by such an excrescence is sometimes very great. The free border of the growth is lined by a row of the round nuclear cells separated by some intercellular substance; the appearance is the same as a marginal row of cells where there are several layers in the acinus, and the appearance in the centre

of the bud-like prominence corresponds also to that of the lower stratum of cells. Where the process is well advanced, the substance of the intra-acinous or intra-canalicular papillary growth is made up of a hyaline matrix with a number of round nuclei and many of the fibre-like or crescentic bodies embedded in it. But papillary processes may be seen which are almost entirely cellular, with some intercellular substance, and others, again, seem to be made up almost entirely of a mucus-like homogeneous substance which stains deeply. Another kind of papillary process has an arborescent structure running rather to the length than the breadth, and these are the cases where the filiform or rod-like cells are most abundant. How those various structures sometimes become true cartilage is not easy to make out, although the fact is undoubted. If a portion of the tumour that has the naked-eye character of cartilage be examined, it will often be found that the cellular elements are quite indistinct in the midst of the hyaline matrix, and the common appearance is that of the crescent or rib-shaped dark-coloured bodies forming one side of what obviously corresponds to the future cartilage capsule. The tissue is, in that respect, not unlike the peculiar cartilage that is found in callus. Finally, there is an occasional development of the cartilaginous tissue into osseous tissue. Some preparations show perfect examples of medullary spaces lined with osteoblasts, and trabeculæ containing bone corpuscles. These appearances are so characteristic that I have occasionally exhibited them as preparations of the normal osteoblastic condition of growing bone.

The bud-like or polypous growths that are so often associated with the myxomatous and cartilaginous transformations are structures that may seem, in their mature form, to bear out the theory of a connective-tissue origin; they correspond to the kind of tumour described as intra-canalicular polypous myxoma, and the dendriform outgrowths, made up largely of rod-like cells, correspond to the intra-canalicular papillary fibromata. But the same transformation is represented in Figs. 35 and 36 as occurring throughout groups of acini, and there is no doubt that the ordinary cellular contents of the acini are the elements that become the subject of it. The cells in the deeper layers of Fig. 35 are exactly the same as occur in the substance of the bud-like growths, and the deeper cells in the former are to be reckoned among the epithelial cells of

the acinus just as much as the more uniform rows of cells on the surface. In the upper acinus of Fig. 35 there is, on one side, a papillary outgrowth of cells, which may be regarded as an early condition of the larger polypous growths that are seen elsewhere; and that papillary outgrowth is obviously of the same kind as the wart-like growths of epithelium in Fig. 28. If the epithelium of the breast were at all times the polyhedric nucleated cells of the lactation period, it would be somewhat irrational to derive a certain class of the morbid structures from it; but if it be borne in mind that the epithelium of the breast, in the course even of its normal periodical processes, assumes a variety of types from stage to stage, and that in its abnormal processes that variety takes a still wider range, it will not appear strange, but on the other hand perfectly reasonable to identify these varieties in the tumours that seem at first sight to have grown from the stroma of the organ. On *a priori* grounds it might be objected that epithelial cells and cells of the connective series are not "equivalents;" but even as an *a priori* argument, that objection is of questionable force. In my paper on the histogenesis of secondary tumours in the liver, printed elsewhere, I stated a number of facts to prove that secondary sarcomatous nodules, no less than secondary epithelial nodules, were formed out of the liver cells at particular points in the organ. Thus the liver-nodules that were secondary to a sarcoma of large and pigmented spindle-cells, primary in the subcutaneous tissue, took origin in a transformation of the liver cells at certain centres of infection; the individual liver cells could be seen to undergo a definite endogenous change, so as to become the ultimate spindle-cells of the tumour. In that case there is no equivalency as between cells of the same type, but there is metaplasia or change of type; and if it be necessary to add a theoretical explanation to the actual description of the myxomatous and cartilaginous growths, that point of theory is supplied by the doctrine of metaplasia which I have already stated in connexion with other varieties of growths in the breast.

With the cartilaginous and myxomatous transformations, I bring to an end the illustrations of morbid physiological action in the mamma of the bitch. I have described, in their physiological order, the processes of tumour-formation in which the large pigmented cells, the somewhat large and granular nuclear cells, and

the mucous cells (with their myxomatous and cartilaginous developments) respectively play a part. The illustrations that have been given relate to the epithelial products both in the tissues outside the acini, and in their original intra-acinous position. The intra-acinous accumulations are of very much the same nature in all varieties of the tumour process; the acini may have more than one layer of cells on their wall, or their cavity may be occupied by cells wholly or partially, or the epithelial lining may run out into villous or papillary processes, or the acinous space may be crossed by trabecular columns of cells.

In making use of the considerable series of cases in the bitch that had been collected as the material of an investigation, two courses were open to follow. Either the tumours might have been fully described one by one with all their attendant circumstances, and, as a final solution of them, they might have been referred to their classes in the tumour-kingdom, after the manner of living things in systematic zoology or botany; or they might have been used collectively to illustrate the various points of tumour-formation. It is the latter course that has been followed, and it may be stated with some confidence that the illustrations of pathological processes, which have been given in their physiological order, do not omit the leading features of any one of the whole series of tumours. On the other hand, the mammary tumours of the bitch do not lend themselves readily to the classification method; they are sometimes multiple in the same case, with varieties of structure in the several centres of disease; and even when there is no multiplicity of centres, the structure throughout the tumour is not always uniform.

As the tumour disease in the bitch differs in some respects from the mammary tumours of ordinary surgical practice, I collected at the same time a number of cancers of the human female breast, to which I shall now briefly refer for comparison. The figures 29 and 30 are taken from a very typical case of cancer in the breast. The patient was a widow, aged 60, who had borne a large family. The tumour was a circumscribed nodule, not more than one inch in diameter, and situated towards the periphery of the gland on the axillary side. The nodule was of firm texture, and it was easily distinguishable from the surrounding tissue by the softer and more parenchymatous character of its structure. According to

the miscroscopic examination, it must be considered to be an intra-acinous formation occurring in a small and isolated portion of the gland. The whole breast was removed in the operation, and the bulk of it, which remained hard and dense after lying in spirit, was made up of close tendon-like bundles of fibrous tissue, with very few traces of epithelial tubes scattered through it at wide intervals. Both in the density of its stroma and in the reduction of its secretory framework, the tissue beside the tumour may be considered to represent the usual condition of the breast in women after the climacteric period. It is at that period of life that the intensely hard tumours of the breast are apt to occur, and the peculiar hardness is probably owing to the nature of the stroma in which the cells, or active elements of the tumour, lie[1]. The present case is an instance of a mammary tumour appearing late in life, but occurring in the form of greatly enlarged acini of the gland. In no other part of the organ was there any appearance of a surviving cluster of acini, or even of the infundibula of ducts. The glandular apparatus had disappeared, except at the point where the morbid action had established itself. I have already referred to the climacteric changes of the breast, although I have not had an opportunity of following them closely; and I observed that the post-climacteric tumours of the mamma were to be considered as morbid growths incidental to the process of effacement of the secreting structure and to the final withdrawal of the secretory force. From that point of view, the origin of the present tumour would be looked for in the survival of some outlying part of the structure, and the correlated persistence of a functional force, while all the rest of the organ had become obsolete.

Fig. 26 is from another case in a woman beyond the climacteric period, the patient's age being 58; it was removed on the same day as the tumour just mentioned, and it offers several points of contrast. The growth was more centrally disposed beneath the nipple, and had not so definite boundaries. A considerable pro-

[1] "Thus we are told that scirrhus is marked and distinguished by its fibrous character: whereas the fibrous appearance, in a great degree, belongs to the normal condition of the organ, and is not a product of the disease. Many other equally erroneous statements might be mentioned, and for this reason I felt that it was absolutely necessary to give an account of the natural structure of the breast, before its morbid changes could be properly explained or understood."—Astley Cooper, Introduction to *Anatomy of the Breast*.

portion of the cells appeared to fill up the surviving tubular framework of the gland, changing it into a system of solid tracts of cells; but a large number of the cells were as if infiltrated into the surrounding stroma, in the manner shown in the figure. The tumour was intensely hard, and may be considered to be a typical case of skirrhus.

A third case, belonging to the same period of life, occurred in a woman aged 56. The new growth was of small extent and situated under the nipple; it was indefinitely bounded, and the stroma of the gland, or at least the substance round the tumour, was chiefly fat-tissue which extended into the tumour area in the form of pointed processes. Unlike the last-mentioned case of post-climacteric cancer, this case showed several very distinct acini, which were enlarged and occupied by anastomosing trabeculæ of somewhat nuclear cells.

A fourth case occurred in a woman aged 54. The ducts of the gland were obviously dilated, and a fluid of greyish colour, like a catarrhal secretion, escaped from them on section. There were in this case none of the usual appearances of an active growth, but, on the other hand, evidences of retrogression or cicatrization. The connective tissue was generally full of small round cells, and resembled the tissue of chronic inflammation. At a number of points of the glandular tissue, there were found concentrically laminated sand-grains, which coloured deep purple with the logwood staining fluid. I have found the same kind of sand-grains in one of the tumour cases in the bitch, and also in a ewe's udder, in which there had been a somewhat disturbed periodical evolution. In the latter case, the sand-grains lay within acini of the gland, and completely filled the acinous space. The occurrence of sand-grains in tumours of the breast has been described as evidence of a retrogressive process[1]; the cicatricial condition of the connective tissue in this case (small-celled infiltration) is also evidence of the innocuous nature of the disorder; and I have to add a third feature pointing to the same conclusion. In the midst of the cicatricial connective-tissue there occurred, at somewhat regular intervals, groups of cells of a totally different kind; they were as large as the full-sized epithelial cells of the breast,

[1] See a case of *Carcinoma atrophicum* of the breast, recorded by Ackermann in the 45th volume of Virchow's *Archiv*.

and the clusters of them no doubt represented the remains of the secreting structure. The point of interest is that each cell was very distinctly vacuolated, having a nucleus of considerable size on its periphery, as in Fig. 17. The vacuolated epithelium has a definite significance in the normal processes of the breast, and there is hardly any doubt that it has a corresponding significance in the pathological. Vacuolation of the epithelium is found in the first of the above four cases from the human subject; the epithelium is accumulated in several layers on the walls of the acini (Fig. 29), and their lumen, where it is not obliterated, is occupied by a number of cells vacuolated to such an extent as to be little more than hollow vesicles. They are the cells of the upper stratum that have come nearest, as it were, to the proper functional activity, and have been thrown into the cavity of the acinus. The well-known mother-cells of cancer exemplify the same degree of functional change; sometimes they contain one or more young cells in their vacuoles, but they often occur in the signet-ring form. It has been pointed out by Virchow that such transformations (degenerations) of cells in cancerous tumours, lead to a partial healing of the disease[1]. It is only another mode of expressing the same fact that the more or less complete transformation of some of its epithelium is the nearest approach to the healthy function that the gland attains to under its diseased circumstances. Atrophic cancer of the breast is a return of the diseased breast to the paths of health. It may be described, also, as the intensifying of a functional excitation that is morbidly weak, or as the raising of the functional force from a dangerous degree of feebleness to a safe degree of strength.

The above-mentioned cases of mammary tumours in women occurred after the climacteric period. I shall now refer briefly to four cases belonging to an earlier period of life. One of them occurred in a widow aged 36. The disease was at first circumscribed and situated in an outlying part of the gland; but from injudicious treatment, the tumour had grown rapidly and protruded through the skin as a fungus. The whole breast was removed at the operation, and the unaffected part of it was found to have very much the same structure that has been described for

[1] *Archiv*, Vol. I. p. 138.

the resting state of the mamma in the bitch. One cluster of greatly enlarged acini occurred in the neighbourhood of the tumour, which showed a distinct approach to the structure of the actual tumour. That structure was of the usual intra-acinous kind; the cells were almost entirely nuclear, and of a large size, and numerous multi-nuclear cells occurred among them. Besides the accumulations of crude epithelium within the acini, there were extensive columns of the same cells in the fibrillar tissue outside.

Another case occurred in a married woman aged 39. Parts of the gland within the tumour area were found little affected; they consisted of lobuli in an extreme state of involution, separated from each other by wide tracts of fibrillar tissue. The lobuli were made up of a number of lateral offshoots or infundibula from a central duct; the cells were of the nuclear kind always found in the resting state of the gland. The growth itself was almost entirely intra-acinous. The acini were not very greatly enlarged, and the cells within them were more of the kind that are found in myxomatous tumours than in medullary cancers; that is to say, many of them were staff-shaped or crescentic elements lying among a homogenous or fluid substance.

A third case, of which the clinical history is wanting, presumably belonged to the same pre-climacteric period of life. The tumour disease extended uniformly over the whole or the greater part of the gland, and the normal lobular subdivisions could be traced. All the acini were of the same size, and not much larger than the acini of the resting state. They were uniformly filled with groups of highly granular nuclear cells, which in some cases were so closely cemented together by intercellular substance as to resemble single multi-nuclear cells, while in other cases there was a small cavity in the centre of the group.

In those three cases, the tumours were of the soft kind; the neighbouring glandular structure, so far as it was examined, had the usual appearance of the periodical resting state; and in two at least of the cases the patients had not reached the climacteric period. I have one more case to mention, which is intermediate between the first group of post-climacteric tumours and the group just described. It occurred in a widow aged 40, and it was a distinctly hard cancer. The acinous structure could be traced

clearly in the tumour, in the form of alveolar spaces. The cells lay loosely within the spaces and appeared to be suspended in a clear fluid. The forms of the cellular elements resembled those already described for the myxomatous transformations in the mamma of the bitch, corresponding to the mucus-producing stage on the physiological scale. Frequently a large nucleus lay as it were free within a cell with a somewhat thickened wall, and the fragments of these cell-walls or cell-membranes were sometimes found separately in the form of crescent-shaped bodies[1].

The study of these mammary tumours of women would not, of itself, have suggested the principles of tumour-formation in the breast, or the illustrations of morbid physiological action, which I have endeavoured to derive from the examination of the tumour disease in the bitch. But if the appearances in the human cancers be interpreted according to the physiology of the breast, normal and morbid, as derived from the latter source, it will probably be admitted that there is nothing in them that involves any additional or different principle of general pathology. It is the climacteric effacement of the breast that gives a peculiar character to the disease in women; and there are well-marked structural differences in the tumours according as they appear before or after that period. Those that develope after the climacteric years are perhaps the most common, as they are certainly the most intractable; they have figured most prominently among the tumours of the breast, and they have been the real source of ambiguity in the pathology of the organ. That ambiguity depends upon the circumstance that they occur in an organ which is gradually losing or has lost its characteristic structure. Where the normal itself is vanishing, the departures from the normal are elusive. The problem becomes all the more complicated when we consider that the effacement of the mammary structure and function, occurring as it does in an organism that is still vigorous in all respects but the sexual, is itself a kind of pathological incident, or at least an event that might very easily assume a pathological character.

[1] "In *Carcinoma alveolare* the walls of those old cells that contain the generations of young cells appear at last to break up and to form distinct fibres, which remain unconnected with one another."—Johannes Müller, *Ueber den feineren Bau der krankhaften Geschwülste*, p. 5.

It will now be convenient to sum up the more general conclusions of the pathological inquiry. From the study of the cases in the bitch, the inference seems justified that the earliest and most general disturbance in the mamma is a kind of spurious evolution from the resting state. The fringes of glandular tissue round the tumours, and the more distant parts when they could be got for examination, were found either in the resting state, or more or less advanced in the process of unfolding. The departures from the resting state were either slight in degree, or, if more extreme, they were limited to small areas. Thus, the production of large granular pigmented cells, indicating the earliest departure from rest, was very generally observed in the tissue near the tumours; in a few cases the margin of gland showed a mixture of all conditions of the acini, from the state of extreme involution to that of full expansion. For example, the two varieties of polyhedric epithelium in Fig. 2 are taken from the tissue near a tumour, most of which was in the upfolded state. Out of the whole collection of cases in the bitch, there is only one in which the neighbouring glandular tissue did not show either the resting condition or limited departures from it. The tumour was a large soft growth having the intra-acinous structure of medullary cancer; the fringes of gland that were removed with it had the parenchymatous appearance of the fully expanded organ, and the minute structure of the acini was uniformly that of the most advanced stage of the periodical evolution. If the animal was pregnant, the condition of the mamma would be at once explained; if pregnancy could not be assumed, the cause of the very regular and extreme state of unfolding is not at all obvious from the pathological point of view. The morbid influence that causes a tumour to form in the breast probably affects the organ elsewhere than at the point of tumour-formation; but the general disturbance of the gland from the resting state is not as a rule carried to any considerable degree.

A circumscribed tumour arises at a particular part of the gland where the spurious excitation has advanced beyond the earlier stages of evolution or unfolding. In that particular region, probably a territory defined by the blood-vessels, the functional force has acted at a uniform imperfect level for a length of time; the inevitable cellular waste of the crude secretion has accumulated within the acini or around them, and the foundation of a tumour has been

laid. The distinguishing feature of the less malignant forms of tumour is that the spurious functional activity comes nearer in the degree of its intensity to that of the perfect secretory force; the transformation of the epithelium is a more real transformation, and the cellular waste is reduced, in part at least, to the class of fibre-like or crescentic elements that characterise the myxomatous and cartilaginous issues of the tumour process. Some of the atrophic or regressive cancers of the breast in women may also be said to depend on a more real vacuolation of the glandular cells.

The circumstance that the unknown diseased excitation most commonly befalls the gland when it is in the state of rest, is of the first importance in accounting for the formation of a tumour. Whether the disturbance be a mechanical injury, or a sympathy with excitement in the ovaries, or of a more general emotional nature, it comes upon the breast in its resting state. The breast can react in no other way than by following the somewhat slow process of its normal evolution; without the intermediate stages of unfolding, it cannot reach the perfect degree of its function in which there would be immunity from danger. The intermediate stages are necessarily associated with the formation of crude cellular products; it is at one or other of the intermediate stages that the morbid force delays, and the corresponding cellular secretion of the gland thereupon assumes the character of a formative or tumour process. With the effects of a disturbance from the resting state, we may contrast the very different effects of a disturbance of the perfect function. When the mamma in its state of full expansion and perfect functional activity becomes the subject of an interference, the result is very commonly a diffuse or nodular inflammation and the formation of abscess. A sudden stoppage of the milk soon after the lactation has been established is apt to produce inflammation, and the same result, or a degree of it, sometimes follows the weaning of the child after a long course of suckling[1]. The disturbing cause, whatever it may be, acts upon the mamma when its function is at the greatest intensity, and the characteristic effect is inflammation and abscess. The precise nature

[1] "The mammary glands often become immensely distended at the time of weaning, and by manipulation hard knots or lumps are discovered...The axillary glands may become painful, swollen, and even advance to suppuration."—Birkett, *Diseases of the Breast*, p. 182.

of the cellular processes that go on in inflammation is still a matter of controversy. According to one view, the leucocytes that are found to crowd the inflamed area are derived in every case from the blood-vessels, being the escaped white corpuscles; according to another view, the leucocytes of an inflamed part may have other origins as well. If reference be made to the figure on page 26, it will be seen that the fibrillar tissue about the acini, and the lymphatic channels encircling them are crowded with leucocytes or lymphoid cells, which are derived from the secreting epithelium. The case was precisely one of those cases where an inflammation of the gland might have been expected; the ewe gave birth to a dead lamb at the full time, and the udder remained unmilked. The figure shows the state of the glandular tissue three weeks after the parturition; there were no actual signs of inflammation, but it is easy to imagine that a more excessive or more general production of the same nuclear cells from the epithelium would have led to the appearances of inflammation and of abscess; and as there exists no theory of inflammation of the breast based on observation, such a process, amounting to a catarrhal state of the secreting parenchyma, is as probable as any other. The small round cells in the figure are products incidental to a somewhat enfeebled secretory activity; they are the characteristic kind of waste product that the epithelium tends to form when the functional excitation is only a little short of its highest intensity. It may therefore be said that a disturbance of the glandular function tends more to transitory inflammations or abscesses and less to permanent cell-collections or tumours, in proportion as the secretory excitation is near its highest intensity and the epithelium of the acini near its perfect form. Contrary to the scholastic maxim in morals, the pathological case may be said to be one of *corruptio optimi optima*[1].

[1] A place may be found here for an observation by Sir Astley Cooper (*The Anatomy of the Breast*, p. 137). "Suckling also diminishes the disposition to malignant diseases of the breast; for although women who have had children are still liable to cancerous and fungoid diseases, yet it is undoubtedly true, that breasts which have been unemployed in suckling, in women who have been married but are childless, and in those who have remained single, are more prone to malignant diseases than those of women who have nursed large families; and if it were only to lessen the probability of the occurrence of such horrible complaints and causes of dissolution, women ought not to refuse to suckle their offspring."

The comparatively safe issue that follows the disturbance of the glandular function at or near its highest intensity, affords an analogy for the comparatively safe or curable tumours of the female breast that are apt to occur between puberty and the age of thirty or thereabout. They are classed by Billroth under the name of sarcoma of the breast, and their characteristic is said to be that they not unfrequently tend to undergo spontaneous resolution[1]. It is also a familiar fact of surgical practice that the same class of tumours of the breast are sometimes dispersed by strapping or by the application of cold, or by other means. On the other hand, by far the greater number of the really intractable tumours of the breast are those that occur at or near the climacteric years. The occurrence of that period in the life of a woman affects the mamma both in a positive and in a negative way. The final stoppage of the menstruation is known to produce certain "sympathetic" movements in the breasts; they sometimes even enlarge and discharge a milky secretion. In many women the sudden disturbances at the climacteric period are probably greater than the organ has experienced for years before. But the real fatality of those climacteric disturbances, and of all subsequent excitations of the organ, is that the breast then suffers an effacement of its secreting mechanism and a withdrawal of its secretory force. If a morbid influence comes upon the breast within the years of sexual maturity, there is always the possibility that the organ may sooner or later throw off the diseased action by a return to its vigorous normal activity. But if the capacity of functional excitation be lost, and the possibility of unfolding finally surrendered, then the played-out organ falls an easy prey to whatever disturbance may reach it through its old physiological channels. If the functional capacity of the breast did not, in the human species, come to an end long before the natural term of life, there would probably be much less risk of intractable tumour-formation; and it is only in those tumours that form in the breast within the period when the function may still be awakened to its full and healthy vigour, that a resolution of the disease, or a dispersion of the diseased products, may be looked for.

In these particulars the liability of the breast to intractable tumours is somewhat special to the human subject. The more

[1] *Chirurgische Pathologie*, p. 700.

general liability to tumour-formation arises out of the general physiological characters of the gland. Its secretion is inevitably cellular throughout a considerable part of its functional existence. The cellular products are incidental to that law of endogenous cell-formation according to which the secretion of the gland appears to be formed; they are not derived from the epithelium by ordinary generation, but they are products of an alien or heteroplastic type. A disorder of function, where the normal arrangements are of such a kind, leads in the most natural way to tumour-formation. The descriptions, in this and in the former chapter, are selected illustrations of the various degrees of disordered function, which have resulted in various kinds of tumours. If there be any new and heterodox pathological doctrine involved therein, that result is at least the outcome of a scientific method. The attempt to illustrate pathology by physiology is according to the best precedents, and whatever novelty there may be in these pathological chapters is a novelty that comes from the physiological side.

CHAPTER VIII.

TUMOUR-INFECTION OF LYMPHATIC GLANDS.

In the two preceding chapters I have endeavoured to show, by references to cellular physiology, that the common tumours of the breast take origin in certain irregularities of the glandular function; the tumour-disease of the breast has been represented to be essentially a disorder of function. From that genetic point of view, the new growths in the breast can hardly be admitted to be things in themselves, capable of being defined *per genus et differentiam*, or referable to the classes of a tumour-kingdom, after the manner of natural objects in the animal or vegetable kingdoms. To make use of a philosophical term, it is not from the ontological point of view that tumours of the breast have been discussed. But, as a matter of practical convenience, the classification of tumours cannot be abandoned; and even in theory we are ultimately driven to regard tumours as things in themselves. However closely we may trace the departures from the normal to which a tumour of the breast owes its origin, there is sooner or later manifested in typical cases of the new growth, a property which is not in any sense a departure from the normal of the organ, but an attribute possessed by or acquired by the tumour as a separate individual. That property is the malignity of the tumour; and the malignity is best seen in the infectiveness of the tumour, or in its tendency to beget its like in the form of secondary tumours throughout the body. The present chapter, relating to the infectiveness of tumours as shown in the infection of lymphatic glands, is therefore complementary to the former chapters, in so far as it

recognises the tumours to be entities or individuals that have the remarkable property of begetting their like.

The investigation on infected lymphatic glands is also related to the rest of the work, in that the process of their infection is as far as possible explained or analysed on the basis of the physiological chapter treating of the lymphatic glands of the breast. When the lymphatic glands are infected with the tumour-disease that is primary in the breast, one naturally refers for an explanation to the kind of relationship that subsists in health between the secreting organ and its lymphatic appendages. It is not for a moment to be expected that so vast a problem as that of infection will find so simple a solution, but the intelligible relationship between the breast and its lymphatic glands offers a convenient means of approaching it. I shall therefore begin with the case of lymphatic glands infected from tumour of the breast, and afterwards proceed to consider the question generally, taking the facts from cases both of epithelial and connective-tissue tumours.

The infected lymphatic glands of which preparations have been made, were derived from upwards of twenty different cases. Several of them were mammary cases, both in the human subject and in the dog and cat. In three cases the primary tumours occurred in the stomach, and in one case the primary seat was the great intestine. The infection of lymphatic glands in cases of sarcoma is sometimes doubted, but there are four cases in this series belonging to that class. One of these, of which I have given a detailed account elsewhere[1], was a tumour growing from the periosteum by the side of the fifth metatarsal bone; a large packet of lymphatic glands in the groin were affected, as well as many retroperitoneal glands. Another was a case of tumour of the upper jaw, containing many large multinuclear cells; in that case also the lymphatic glands within the abdomen were everywhere enlarged and changed into tumour-tissue. The other sarcomatous cases were a scapular tumour (in the dog), and a periosteal tumour of the tibia recurrent in the pelvis. The collection included also a number of miscellaneous cases, of which the most remarkable and the most instructive was a case (in the dog) of liver-tumour that appeared to be primary, with secondary infection of portal and mesenteric glands.

[1] *Journal of Anatomy and Physiology* for April, 1878.

Many of the cases had secondary tumours of the liver or lung, or of both organs, and in one case (sarcoma of metatarsus) both ovaries were infected with the tumour-disease. I have made use of the whole of this material in my investigation, but I shall confine myself, in this digest, to the description of a few typical cases.

The one generalisation that stands out conspicuously from the examination of the whole collection of cases is that the secondary tumours (of lymphatic glands and other organs) correspond in structure to the primary, even in the most minute particulars. There are no doubt some cases in which the identity is not perfectly obvious; but in the great majority of cases the resemblance or mimicry is carried to so great an extent, that it is not possible to mistake the significance of it. This well-established fact of a minute resemblance between the primary tumour and its secondary or infective products, affords at the outset an invaluable clue to the nature of the infective process as regards tumours; and the tumour-infective process, marked as it is by definite structural features, may be justly regarded as an index of infection in general. By establishing a resemblance or family likeness between a primary tumour and its secondary products, we are led to conclude that the infectiveness of primary tumours is a property that they develope of themselves; no agency from without can be thought of, which might call into existence an infection carrying with it so particular—one may say, so autochthonous—points of structure.

In illustrating further the infectiveness of a tumour, it will be useful to revert for a moment to the physiological interpretation that has been applied, in the previous chapters, to tumours of the breast. The primary tumour is the mammary gland, or a portion of the gland, more or less modified in its structure through aberrations of its function. The functional disturbances are never exactly the same in any two cases, and the respective modifications of structure, or, in other words, the structures of the respective tumours, are never exactly the same. Although there are necessarily more points of likeness than of unlikeness in two cases of tumours of the same organ, arising at corresponding periods of life, or under corresponding circumstances generally, yet each tumour has its distinct individuality. There are the same differences among individual tumours as there are among individual

persons. Now, it is the individuality of the tumour that is reproduced in the secondary tumour. That fact is so remarkable that the attention is at once arrested by it, and it is no less striking as a phenomenon than significant as a point of argument. If the secondary tumour reflects the individuality of the primary, it is obvious that the infective influence emanates from the primary tumour, and that it is a property of the latter developed within it, and independent of all extraneous influences. Whatever the nature of the infection may be, it appears certain that it is derived in the most intimate way from the primarily diseased part. In other words, the infectiveness of a tumour is a property of the cellular elements of the tumour and of their juices.

The subject of lymphatic-gland infection has not hitherto engaged a great deal of attention, but there have been a few important contributions to our knowledge of it within the last twenty years. In particular, Billroth has made investigations of the lymphatic glands in a variety of infective processes, including, among others, those of acute inflammation, scrofulosis, typhoid fever, and cancer[1]. The infected mesenteric glands in typhoid fever were studied by Virchow, and compared with the lymphatic glands in other infective processes[2]. The infection of axillary lymphatic glands in a case of cancer of the breast has been described by W. Müller[3]. The general question of lymphatic gland-infection has also been treated of by Hansen[4], with special reference to leprosy and scrofula. A more than usually elaborate account of the infection of bronchial glands in a case of cancer of the œsophagus has been published by Gussenbauer[5]. It will not be necessary, in the sequel, to refer otherwise than in general terms to the conclusions of these writers.

In proceeding to the details of this investigation, it will be convenient to take first the cases of mammary tumours in the bitch, where the lymphatic glands, especially those beneath the inguinal portion of the mamma, were affected with the disease.

[1] *Beiträge zur pathologischen Histologie*, Berlin, 1858; and in *Virchow's Archiv*, Vol. 21.

[2] *Würzburger Verhandl.* I. 86.

[3] *Henle und Pfeufer's Zeitschrift*, 1863.

[4] In a memoir published at Christiania, 1871.

[5] *Archiv für Klinische Chirurgie*, 1872.

In the third chapter I described at length the nature of the physiological relation between the secreting gland and its lymphatic glands. The lymphatic gland was a kind of depuratory apparatus, receiving the cellular waste of the secreting gland, and reducing it to the uniform condition of lymphoid cells. The most noticeable and unmistakeable form of waste cells were large nucleated granular cells, containing a yellow or brown pigment. Those cells, being waste products of the imperfect secretion, were conveyed to the neighbouring lymphatic glands in large numbers, and in many preparations they could be seen occupying the lymph-sinuses. The pigmentation of the cells enabled them to be traced easily from their origin within the acini to their final disposal and utilisation in the lymphatic gland. Such, then, being the well-marked relation between the secreting gland and its lymphatic appendage in health, the question naturally arises whether the "infection" of the lymphatic gland from a diseased mamma is in any way dependent on a modification of the health relationship. If that should prove to be so, the infection of the lymphatic gland would be placed on a different footing from the infection of the liver, as described by me in another paper. The liver substance is nothing more than a convenient soil for the infective process to plant itself upon; whereas the lymphatic glands near the mamma are not merely dense masses of parenchyma liable to be attacked by the infection, but they are also physiological adjuncts of the primarily diseased organs, and part and parcel of the secretory apparatus. It will therefore be a first subject of inquiry, whether the infection of the mammary lymphatic glands is in any way incidental to the collecting and purifying part that they play towards the waste products of the secreting gland.

One case may be taken as an illustration of the problem here presented. The tumour occurred in a bitch at the inguinal end of the mamma on one side. It consisted mainly of a thickening of a small part of the mamma and of one or two circumscribed small nodules. In removing the affected part of the mamma, it was found that a cluster of lymphatic glands, lying immediately beneath the mamma and embedded in fat, were both enlarged and otherwise changed; and they were removed adhering to the tumour along with some of their surrounding fat. Two of them were about half-an-inch long and somewhat less in their shorter

axis. On cutting them open there were differences at once apparent in their substance, certain tracts being deeply pigmented and denser, while other parts were free from pigment and more elastic. The microscopic examination showed in various places a definite new formation. The new structure generally existed within the limits of a follicle. There were two varieties of it. One of them was a structure composed of large rounded spaces lined with a kind of cubical epithelium with large nuclei. This structure closely resembled the appearances in certain parts of the primary new growth. The new structure in another of the lymphatic glands was different. It consisted of long columns of epithelial-like cells, extending into the central clear space of the follicles with their extremities free, or forming a network of trabeculæ crossing the area of the follicle. That kind of structure is quite definite and is often found in mammary tumours of the bitch; in this case the primary tumour, or the diseased portion of mamma, did not show precisely those appearances at any part of it that was examined, but it showed a papillary kind of structure that had doubtless grown out of an earlier form such as that found in the lymphatic gland.

Leaving as it stands the question of resemblance between the primary structure and that in the lymphatic glands, we may turn to consider how the new structure in the lymphatic glands was acquired. The glands, it has been said, were obviously pigmented more at some parts than at others. In the normal condition, the same lymphatic glands are often found to have their lymph-sinuses occupied by large granular pigmented cells, and the follicles are sometimes found to be strewn with grains of free pigment. In this pathological case, the most noticeable point of difference is that the large round pigmented cells have overflowed from the lymph-sinus into the substance of the follicle. But there are certain other changes in the diseased gland which may or may not be antecedent to, or the cause of, the overflow of mammary cells from the lymph-sinuses into the follicles. The lymph-sinuses themselves are often seen to be more obstructed by their contents than normally. The fibres stretching across them and forming their filtering or depuratory apparatus are broader and thicker, and the pigmented cells that ordinarily pass through them, and become stripped of their pigment and cell-substance in so doing,

appear to have taken up as if permanent positions; the lymph-passage is in fact clogged up. There is, however, a more general change in the parenchyma of the gland, of which the change in the lymph-sinuses is perhaps only a part. Throughout the whole of the gland the lymphoid cells have become swollen. In ordinary circumstances, and under ordinary methods of preparation, the lymphoid cells appear as naked nuclei. In the beginning of the infective cancerous process, they are all found to have a narrow but distinct investment of protoplasm; the nucleus is now surrounded by a margin of cell-substance, and the closely-packed cells of the follicles have often a rectangular or polyhedric shape, resembling epithelium. The swelling of the parenchyma is quite general throughout the gland, and it is difficult to say by what agency, issuing from the seat of primary disease, it may have been brought about. The swelling of the parenchyma of the secondarily infected organ appears to be the first step in the process of cancerous infection.

The swelling of the lymphatic parenchyma is not peculiar to the infective process of malignant tumours. It occurs, generally speaking, in every infective process, including acute and subacute inflammation, scrofula, tuberculosis, syphilis, typhoid fever, &c. The resemblance in their initial stage between certain of these processes was made out by Virchow, and between others by Billroth; so that it may be said to amount to a generalisation. In the cases of infected mammary lymphatic glands, it is difficult to decide whether the swelling of the lymphoid cells of the parenchyma preceded or followed the overflow of cells from the primarily diseased part into the follicle, and it remains therefore doubtful how far these cells, by their contact or otherwise, were the agents of infection. But whatever the cells brought from the diseased mamma may have had to do with the initial swelling of the parenchyma, which is common to this particular infective process and to every other infective process, there is little doubt that they sometimes determine the permanent structural changes in the cancerously-affected lymphatic gland.

To return to the case of lymphatic gland beneath the diseased mamma of the bitch. The new growth in the lymphatic gland consisted, in some places, of papilliform processes or trabeculæ of epithelial-like cells, resembling a structure of common occurrence

in primary mammary tumours. In the primary disease, that structure is dependent on outgrowths of the epithelium lining the acini; several varieties of this primary process in the mamma were described and figured in the sixth chapter. In the secondarily affected lymphatic gland, the same papilliform processes and trabeculæ occur, and they appear to arise from the wall of acinus-like cavities, just as they did in the acinous gland. How then does the lymphatic gland assume this wonderful imitation of the pathological process in the secreting gland?

In the first place, it is the dense parenchyma of the follicles and cylinders that is the seat of the changes; the lymph-sinuses may be disregarded for the present. The lymphoid cells of the follicles, it has already been pointed out, have acquired an investment of protoplasm or a fringe of cell-substance round the nucleus. As in the first stage of all the infective processes, the lymphoid cells have acquired something of an epithelial character. In other infective processes the swelling of the parenchyma is only a passing phase; the swollen cells undergo rapid changes either in the way of suppuration or of necrosis, and the process, if it runs its course, ends in cicatrization. The tumour-process is eventually distinguished from all of these; although in some of the cases of tumours, to be afterwards mentioned, there is a resemblance with other infective process beyond the point of parenchymatous swelling. In the particular case, however, that has been selected for the general description, the lymphoid cells permanently retain their protoplasmic investment, and become endowed from that time forward with the persistent vitality and power of increase which distinguishes tumour-cells.

Up to this point we have found that the cells of the whole follicle become uniformly changed into epithelial-like cells. It is out of that matrix-tissue that a particular structure is carved, according to the pattern of the primary tumour. The compact follicle becomes changed into an acinus-like cavity, with papillary processes rising from its margin (or its floor), and projecting free into its space, or with trabecular bands crossing it in various directions. The carving out of the tumour-pattern from the compact cells of the follicle is effected by means of the large granular pigmented cells. These, it has been mentioned, overflow from the lymph-sinuses into the follicles. They are frequently seen lying

among the cells of the follicles, and in favourable specimens their agency in transforming the follicle into a portion of new growth, after the primary pattern, can be inferred in a general way. Many of them become distended, a cavity forming in their substance; they are thus transformed into large vesicles, which occupy corresponding spaces among the follicular cells. The vesicles then break down, and the follicular cells remain as epithelial-like processes or trabeculæ, with spaces between them, and looking as if they had grown up from the rows of cells lining the wall of a cavity. In the primary tumour the round spaces, with numerous knob-like or papillary projections, are actual acini of the gland, the lining epithelium of which has taken on the common form of papillary overgrowth. Exactly the same appearance is produced as a secondary result in the adjacent lymphatic gland; and the striking resemblance, or rather the exact copy, is effected by carving the pattern out of the compact mass of cells of the follicle. The carving-out process is accomplished by means of a particular class of cells, which are themselves destroyed in the process. Now the large pigmented cells, through whose agency the pattern of the primary tumour is imprinted on the secondarily affected lymphatic gland, are derived from the primary tumour, or, in other words, are products of the primarily diseased organ.

That is, however, only one of the ways in which the lymphatic gland is transformed into the likeness of the primary tumour. Another mode, which is an interesting modification of the first, is as follows. It has been observed especially well in the affected lymphatic glands of a case of mammary tumour of the human subject. The primary tumour in this case is figured on page 143 and again on page 144. It is essentially of the same trabecular structure as the mammary tumour of the bitch just described; the enlarged acini are traversed by anastomosing columns of cells. The structure of the axillary lymphatic gland is of exactly the same kind; there is observed in the primary tumour at certain places a quantity of brown pigment-granules, and collections of red blood-corpuscles, and even in these small and, as it were, accidental circumstances, the lymphatic gland resembles the growth in the mamma. The development of the new growth can be traced through various stages. The first stage is that of general swelling of the parenchyma, depending not so much in this case on a distinct fringe of

protoplasm round the previously naked nuclear lymphoid cell, as upon a uniform enlargement of the lymphoid cell in its nuclear state, the cell becoming at the same time more granular. The next stage resembles that found in other infective processes. The swollen parenchyma appears to undergo a general decay or necrosis. The swollen cells assume an opaque appearance, and fail to colour with the logwood staining fluid. In the other infective processes that stage goes on to the general breaking down of the parenchyma, but in the tumour process the sequel is different. Along certain regular lines throughout the follicle the opaque and, as it were, necrotic cells show a small and brightly-coloured nucleus or nucleolus in their centre. These nuclei are in many cases quite minute points, and such is no doubt their first appearance as young cells in the substance of the old follicular cells. They appear, as has been said, along certain regular lines; and growing up from the old cells along the lines that are as if laid down or marked out for them, they result in a new growth of a definite pattern, the pattern being the structure of the primary tumour. There is in this case, as in the former case, a carving out of the new growth from the compact cells of the swollen follicle, but the carving out is here affected by a residual process. The old cells of the follicle decay except along the lines of the new pattern; and along these lines young cells spring from the substance of the old follicular cells, and in course of time grow up into the form and arrangement of the cells in the primary structure.

A third example of the mode of transformation of the lymphatic gland-substance is found in the epigastric glands in a case of cancer of the stomach. In the primary tumour the epithelial-like cells were collected in alveolar groups in the submucous and muscular coats. The cells lay in the alveolar spaces, packed together without any very definite arrangement. The appearance of the primary structure is simulated in the lymphatic gland in the following way. There is first of all the swelling of the parenchyma; the swollen lymphoid cells then become opaque; and ultimately there arise from them, not along particular lines, but over continuous areas, small young cells, which form the alveolar groups corresponding to those of the primary tumour. But the special interest of this case is in showing the exact mode of origin of the young cells from the opaque and decaying follicular cells. The mode of origin

is here clearly seen to be that of endogenous cell-formation. The young cell lies in a cavity of the parent cell; the smallest of them are minute points like a small nucleus, but even at that stage they seem to lie free in a cavity or vacuole. All the lymphoid cells of the follicle appear to undergo this transformation, and the pale outlines of the old cells can always be seen lying among the endogenous brood, even when the latter have reached a considerable size and become independent. I have already described this variety of endogenous cell-formation in my former paper, treating of the development of secondary tumours in the liver. In the present case of cancer of the stomach, there were affected lymphatic glands of various sizes. It is in the smaller glands that the histogenesis of the new growth can be traced; in a large pigmented gland, the size of a pigeon's egg, the tumour-structure was perfect and finished, and the cells had everywhere their epithelial form and arrangement.

The three cases hitherto mentioned are cases where the semblance of the primary tumour was produced in the lymphatic gland by a process of adaptation or carving out of the lymphoid parenchyma. I shall add a fourth case to illustrate the extreme form of this mode of infection. It is a case of a large sarcomatous tumour in the dog, growing from the ventral surface of the scapula. The brachial plexus of nerves was carried inwards by it, and spread out over its axillary surface, where the nerves, widely separated from each other, appeared to bind it down like the cording of a bale. The lymphatic glands were embedded in the substance of the tumour at its axillary periphery. They could be shelled out from the tumour proper, and they were also distinguishable by their colour and density. There were at least half-a-dozen of these embedded lymphatic glands, and they were upwards of half-an-inch in their longest axis. On examining them, they were found to be uniformly affected, and to be changed throughout into the likeness of the sarcoma which had enclosed them. In some, the process of transformation could be traced; in others the process was complete, the individual cells having lost everywhere their lymphoid character, and assumed the size and form of the tumour-cells. So far as the preparations went, the process seemed to have befallen the lymphatic glands uniformly throughout their substance. The lymphatic glands were, for the

infective process, nothing else than compact cellular masses presenting at all points an equally favourable soil for the infection. The case may be taken as an example of those in which the physiological arrangements of the gland, the relation of the lymph-sinuses to the follicles, and the like, go for nothing. The lymphatic gland falls a prey to the infective process as if it had been a crude mass of cells, and as if its complex structure and its perfect mechanism were non-existent. The infection of inguinal and retroperitoneal lymphatic glands in a case of sarcoma of the metatarsus is of the same sweeping and direct kind.

In such cases it appears hopeless to follow the path of the infection, or to inquire whether it came to the lymphatic gland in the form of a fluid or in the form of cells, or to attempt to analyse the nature of its action on the lymphatic parenchyma. But if the mode of infection in the last of the four cases, and in other cases, chiefly sarcomatous, that might have been given, seems to baffle all analysis and to be referable only to an inscrutable agency, it borders on modes of infection in other cases that are less and less mysterious. The four cases given as examples all show that the infection acted upon the predominant cells of the gland, or upon the lymphatic parenchyma; and in the first of them the cooperation, in the infective process, of cells derived from the primarily diseased part, or the primary tumour, was undoubted. It is this co-operating or determining agency that has to be further inquired into.

In the first of the four cases, the cells derived from the primarily diseased part were large granular pigmented cells. Those cells are normal products of the mammary secretion at its periodically enfeebled periods, and in the tumour processes of the bitch they are produced in unusual quantity at unusual times. They sometimes contribute largely to the bulk of tumours, being collected in heaps outside the secreting acini; and when they are stripped of their pigmented cell-substance, their nuclei subdivide and multiply in the usual way. In the healthy condition of the mammary function, they are conveyed to the neighbouring lymphatic glands, in whose lymph-sinuses they are reduced to a nuclear or lymphoid condition, and are so utilised as lymph-corpuscles. Now, in the pathological states of the mammary function, as they may be studied in the bitch, the lymphatic glands may continue to perform this task for the waste products of the secreting gland

for a considerable time after the pathological process in the mamma has been firmly rooted. In the present collection of mammary tumour-cases there are several in which the lymphatic glands of the mamma, both at the inguinal and axillary ends of the gland, show the normal relations of all their parts; the follicles contain the ordinary lymphoid cells, and the sinuses are filled with the large yellow mammary cells. But it appears that a time comes when the depuratory apparatus of the lymphatic gland breaks down.

The first evidence of failure is stagnation of the large granular cells in the lymph-sinuses, and that is followed by an overflow of them into the substance of the follicles. This overflow may be observed in many cases, and there is no doubt of its close connexion with the process of infection. Side by side with the overflow, there is observed a change in the constant elements of the lymphatic gland. That change is the parenchymatous swelling before mentioned, and it is difficult to say whether the parenchymatous swelling of the constant elements of the gland is the cause or the effect of the overflow of waste cells that are in process of passing through it. The swelling affects not only the lymphoid cells of the follicular tissue, but much more the "fibres" of the lymph-sinus. These fibres are protoplasmic bands, and the nuclei that they appear to contain are merely the circulating cells of the lymph-sinus in more or less close apposition to them. At the same time that the lymphoid cells of the follicular tissue become individually larger or more invested with cell-substance, the "fibres" swell up into broad bands, diminishing the meshes between them. The lymph-sinus thus appears as if it were clogged, and the depuratory process by which the waste cells are reduced to a nuclear state appears as if arrested. It is then that the cells brought from the mamma overflow into the follicles. The real difference between this pathological process and the normal process is that, in the latter, the waste cells of the secretion are received into the follicle only after they have undergone the depuratory and reducing process of the lymph-sinuses; while in the pathological case they enter the parenchyma of the gland in the form of waste cells, and with all the properties of waste cells clinging to them, whatever those properties may be. Having reached the follicles in the condition in which they left the mamma, they

there play a distinct part in producing the semblance of the primary tumour in the lymphatic gland.

In the first case mentioned, the foreign cells determined the pattern of the new growth, or aided in the carving out of that pattern, while they themselves did not go to make up its bulk. But there is reason to think, from a number of other cases, that the waste cells from the primarily affected part may themselves contribute by their own substance to the production of the pathological structure in the lymphatic gland.

The two modes of infection have been discussed by previous writers, and have been broadly contrasted, and treated as supporting rival theories. Either the lymphatic gland is transformed throughout its whole substance into the likeness of the primary tumour, or certain fragments from the primary tumour are carried into the lymphatic gland where they find a lodgment and grow up into a tumour-mass, gradually encroaching upon and causing the atrophy or disappearance of the lymphatic tissue proper. The four cases already given as examples are all illustrative of the first theory; but other cases might be given that would appear to support the second.

The same apparent discrepancy or want of agreement occurs throughout the entire literature of this subject, and not only as between different observers, but as between the different observations of the same observer. Thus Professor Billroth, in his earliest papers on this subject, wrote :—"As regards the extension of cancers by the lymph-stream, I cannot entirely share the opinion of those who here assume a direct transport of cancer-cells, which are merely conveyed to another place, there to fulfil their destiny. This view is to me somewhat incomprehensible; I might almost say, it is conceived too much in the sense of plant-life. In the widest estimate that I can form of the vital powers of cells, I cannot imagine that they swim in the lymph-stream, like fish in the water, or that, like wandering spores, they require only to fix themselves in order to grow up into new individuals. It is much more conceivable that the serum (intercellular substance) conveyed from the cancer has a certain infectiveness for other cells, and that thereby a new diseased process arises in a neighbouring part[1]." Professor Billroth returned to the subject in a later investigation, in which

[1] *Beiträge zur pathologischen Histologie*, p. 201-2.

he had the advantage of newer observations on the lymph-circulation through the gland; and in a case of pigmented cancer of the breast he found melanotic cells in the lymph-sinuses of the axillary lymphatic glands, and was disposed to conclude that these were the starting point of the secondary new growth. He especially remarks upon the value of pigmented cells in tracking the infective process. "By making out," he continues, "that the cancer-formation in the lymphatic glands follows the lymph-sinus, that is to say, the normal lymph-stream, we are again brought face to face with the notion of a transporting of cancer-cells. It appears extremely plausible, from this discovery, that the cells from the cancer reach the lymphatic glands by the lymphatic vessels, and that they there fix themselves and establish a new centre (*Heerd*). But proof is wanting that cells of this kind can be transported, or that they are actually found in the afferent lymphatic vessels of the gland[1]."

In the present collection of cases are several in which the new growth begins in the lymph-sinuses. Thus, in a lymphatic gland beneath a mammary tumour in the cat, the new structure is found at only a few points in the cortical lymph-sinuses; at these points the fibres of the reticulum appeared to constitute the framework of the new growth. In a lumbar lymphatic gland infected from cancer of the rectum, many cells, that can be traced into their ultimate form of tumour-cells, lie in the lymph-sinuses, and where collections of them occur in the follicular tissue, the collections are always definitely circumscribed. Again, in the case of lymphatic glands infected from one of the cases of cancer of the stomach, there may be seen in different preparations, various degrees of encroachment of the tumour-cells from the lymph-sinuses upon the follicles. But many of the lymphoid cells of the follicles retain their lymphoid character to the last, and narrow tracts of them can here and there be seen extending through a gland that is otherwise completely changed into the likeness of the new growth.

In a large collection of infected lymphatic glands from various kinds of tumours, there is no doubt a considerable want of uniformity in the process of infection. But it may well be doubted whether the appearances can be placed in two distinct categories, or be taken to establish two distinct processes. The discrepancies

[1] *Virchow's Archiv*, Vol. xxi. pp. 441-2.

between the accounts of different observers and between the different accounts of the same observer, depend, without doubt, upon differences really existing. The inference from them, at the utmost, would be that there is more than one mode of infection. But a closer examination seems to show that the process of infection in lymphatic glands is in all cases one and the same. The differences depend upon the greater or less degree of intensity of the infection. Those differences in intensity are often exemplified in the same case. It is not uncommon to meet with several lymphatic glands affected, and these of various sizes, say from the size of a pea to that of a pigeon's egg. The smaller glands contain more of the normal structure than the large, and from that circumstance it might appear as if the larger glands, as found, had been the first attacked, and that in them the new growth had spread farthest. But the most usual difference between the larger and smaller glands appears to be that the larger had from the beginning undergone a more extensive or a more general initial swelling of their parenchyma, whereas the smaller are only affected at limited spots. And that difference may be said to depend on the initial intensity of the infection.

It is by keeping this circumstance in view that the apparently irreconcileable varieties of the infective process can be shown to be one and the same. There is not one class of cases in which there is a general transformation of the lymphatic tissue into tumour-tissue, and another class of cases in which the tumour-tissue of the lymphatic gland is derived from the multiplication of primary tumour-cells conveyed thither. But there are extreme cases in which the whole parenchyma of the gland appears to be infected at once by some infective agency which cannot be traced; there are less extreme cases where the whole follicular tissue is transformed by means of cells overflowing into the parenchyma from the lymph-sinuses; and there are cases of feebler infection where the lymph-sinuses are the starting point, and where the transformation proceeds from them throughout the follicle as if in successive zones or from successive centres. The last-mentioned cases are those in which the new growth has seemed to depend on a multiplication of the transported primary cells, and a gradual encroachment upon and supplanting of the normal lymphatic-tissue by them. There is no doubt an encroachment; but it is not a

supplanting and displacing encroachment, but a transforming encroachment.

It will now be necessary to give a digest of the detailed observations on which the above conclusion is based. In the first of the group of four cases, it was stated that the new growth was carved out of the swollen parenchyma or follicular tissue, by the agency of large granular pigmented cells that had overflowed from the lymph-sinuses. More particularly, it was by the vacuolation of these foreign cells that the lymphatic parenchyma was adapted, or transformed into the pattern of the new growth. It is to be observed here that there was no vacuolation of the individual cells of the lymphatic parenchyma. The vacuolation or endogenous cell-formation process has been shown in my former paper to be the mode of transformation of the liver parenchyma in secondary tumours, and the same vacuolation of the individual cells of the lymphatic parenchyma is now to be described for certain of the lymphatic glands. In the first case, there was a process of vacuolation, but it took place in the foreign or transported cells; and as the proper cells of the parenchyma were not transformed by that process, the foreign cells overflowing into the parenchyma may be imagined to have undergone the vacuolation process, as it were, instead of the cells of the part.

The vacuolation process, as an element of the process of tumour-infection, can be nowhere seen more perfectly or more unambiguously than in certain cases of infected lymphatic glands. Vacuolated cells are found in lymph-sinuses, while the follicles are still in their lymphoid condition. Again, the large protoplasmic cells in which the vacuolation process takes place are found to have overflowed into the follicles. Sometimes the vacuolating cells form an outer zone to the follicle, at other times they form definite groups in the follicular substance. The products of the vacuolation are the tumour-elements. In some cases a numerous brood of young cells is found within the cavity of the parent-cell. In lymphatic glands affected in cases of cancer of the stomach and cancer of the rectum, the multiplication of nuclei within the cavity of the parent-cell can be observed. It is obviously the same process as that described as follows by Virchow for scrofulous glands[1]: "In the lymphatic glands the first stage of the process is a very remark-

[1] *Würzburger Verhandlungen*, Vol. I. p. 85.

able hypertrophy of the elements by endogenous formation of nuclei. While the cells increase in size five or six times, it is seen that their nuclei multiply in pairs, probably by a division pairwise, so that as many as twelve pairs of various sizes may be counted in the same cell." It may be mentioned that the largest number of endogenous nuclei in single cells occurred, in the present series of preparations, in a case of secondary tumour in the lung of the cat, after cancer of the breast. The cells lay within the lung alveoli, and appeared to be the swollen cells of the alveolar epithelium. A large endogenous brood is however the exception. The most common case is where the vacuolated cell carries an oblong or crescentic nucleus-like body on one side. It is this body, becoming disengaged, that forms the tumour element. Now, the vacuolation or endogenous process is sufficiently characteristic to be traced. It is first seen in large protoplasmic cells lying in the lymph-sinuses; it is then seen in groups of the same cells at scattered points in the midst of a follicle; and lastly, it is seen all over the follicle. In the last-mentioned stage, it is quite obvious that the cells generally undergoing the vacuolation process are none other than the enlarged lymphoid cells themselves. The lymphoid cells swell up, become granular and vacuolate, and thus the transformation into tumour-cells becomes general.

But the question of greatest interest remains, Do all the cells that are seen in the infected lymphatic gland undergoing the vacuolation process, belong to the pre-existing elements of the gland, or are some of them conveyed to the gland from without? Again, if there are foreign cells among them, how are they distinguishable from, and what is their relation to, those cells of the part that undergo the same process? It is here that it seems possible to reconcile the discrepancies in the different accounts of lymphatic gland-infection.

As regards the lymphatic glands infected from mammary tumours in the bitch, it is possible to speak definitely on the point now at issue, for the large round cells filled with yellow or brown pigment have been shown, in the third chapter, to be normal waste products of the mammary secretion. In health these waste products are conveyed to the lymphatic gland and are there disposed of; in disease they are conveyed to the lymphatic gland and play a conspicuous part in the infective process. Their agency in

carving out the pattern of the primary tumour from the swollen substance of the lymphatic gland has been already described. Leaving the mammary cases for a time, let us consider cases of the stomach and intestine as illustrating a variety of the process. In the affected lymphatic glands in cases of cancer of the stomach and cancer of the rectum, there are found cells exactly analogous to the large yellow cells in the mammary cases in the bitch. They are large rounded cells, with the peculiar protoplasm of the glandular epithelium of the digestive tract. In the case of the stomach, there is every reason to think that they are collateral cellular products of the secretion, in the same way that the large yellow cells are waste products of the mammary epithelium. It is of such epithelial waste cells, or bye-products of the secretion, that the tumours of secreting structures are composed; and the cells that are conveyed to the lymphatic gland are not so much tumour-cells, but cells of the primarily diseased part, which, if they had remained in their habitat, would have become tumour-cells. They would have become elements of the primary tumour after undergoing a more or less obvious transformation, and they become elements of the secondary tumour by fulfilling the same destiny in their new position. So far, there is no infection, but a mere change of locality. But their presence in the lymphatic gland leads to a transformation of the cells among which they lie. Whenever the imported cells overflow into the follicles, the cells of the follicle begin to undergo the tumour-transformation. There are two very instructive varieties in this process, which have been adverted to already. In the one, the foreign cells overflow, and are the agents of carving out or determining the exact copy of the primary tumour. This they do by becoming vacuolated and leaving a space in their room, the cells of the lymphatic gland undergoing all the while a direct or non-vacuolar transformation. The foreign cells contribute nothing to the new growth, except its form. The other variety is in striking contrast to this. The foreign cells overflow into the follicles, and there, as well as in the lymph-sinuses, they undergo that endogenous process by which they become the elements of the new growth. They induce the same endogenous process in the lymphoid cells near them, and both contribute *pari passu* to the building up of the substance of the new growth. In this case there is direct vacuolation of every single cell; but in the other case the

vacuolation takes place only in the foreign cells, and it may be held, even if it be no more than a fancy, that the vacuolation of a few cells stands for the vacuolation of the whole number of cells, so that the transformation of the latter is not round about, but direct. In the one case, also, the initial parenchymatous swelling of the lymphatic follicle took place all over the gland at once; but in those cases where the individual vacuolation of the follicular cells is observed, the parenchymatous swelling appears to break out in limited zones or islands of the gland, and to be in fact the immediate precursor of the vacuolation process in each cell.

The simplest mode of infection may therefore be said to be that in which a considerable number of cells are conveyed from the primarily diseased part to the lymphatic gland, where they themselves undergo a transformation to tumour-cells, and at the same time induce, by contact or by some other unknown influence, a similar transformation in the proper cells of the part[1]. The case of gonorrhœal pus conveyed to the conjunctiva and setting up a purulent formation there, is so far analogous. The analogy appears to hold good to this extent, that as gonorrhœal pus produces gonorrhœal pus, so tumour-cells produce tumour-cells; the chief difference being that gonorrhœal inflammation is morphologically a simple process, while a tumour-process implies the formation of a more or less complex organoid growth.

The mode of infection that comes next in complexity and in obscurity is where a few cells overflow into the lymphatic parenchyma, and determine the transformation of all the cells of the part within a certain radius. There are two instructive points of difference between this case and the last. The few cells that are the agents of infection do not appear to contribute to the substance of the secondary formation, and the cells of the part which alone form the new growth do not, in some cases at least, undergo the characteristic endogenous transformation. But the few infecting cells undergo this transformation, and they may be said to take the transformation upon them, as representing the whole number

[1] With regard to the large quantity of infecting substance, it is worthy of notice that the seminal material, which may be compared to an infective substance, is not produced in merely infinitesimal quantities, but generally in great abundance. See Darwin's Hypothesis of Pangenesis, in his *Variation of Animals and Plants*, Vol. II. p. 363.

of cells of the part. Through the efficacy of the imported cells, the lymphoid cells of the lymphatic gland assume more or less directly the structure of the primary tumour. Now, it is this direct transformation of the secondary parenchyma into the likeness of the primary tumour, that is characteristic of some of the most malignant or intense tumour-infections, and it may be said to distinguish sarcomatous tumours as a class, where those tumours do have the lymphatic glands affected. In such cases it is difficult to trace any transport of infecting cells. The whole parenchyma appears to transform itself directly into the likeness of the parent tumour, as if through some unseen and inscrutable agency. But that agency need not be assumed to differ in kind from the vicarious or substitutive agency of certain cells in other cases, which appears to be associated with the directness of the change into the tumour-tissue. If a few cells originating in, and physiologically belonging to the primarily diseased part, can determine the transformation of a lymphatic gland by being conveyed to it, but without contributing by their own substance to its new structure, then it is conceivable that a similar influence may operate on the lymphatic parenchyma from a still greater distance, that is to say, from the original habitat of the cells in the primarily diseased part. Certain it is that in tumour-infection we are warranted in assuming no other agency than is contained among the properties of the cell, however obscure those properties may be. The mode of action of the spermatic elements is a mystery large enough to cover all the varieties of infective influence residing in cells, and to make them seem intelligible by comparison. But the problem of tumour-infection presents more points of approach than does the mystery of generation. The spermatic influence is, in its effect, one and indivisible, while the infective influence of parent-tumours may vary infinitely in degree. It is from such of these variations as have come under notice in the present investigation that a certain amount of explanation appears to have been reached. In the simplest form, glandular cells of the mamma or the stomach, which would have in time contributed to the primary new growth, are conveyed, by the physiological channels, to the lymphatic gland; in their changed situation they not only fulfil their destiny and become tumour-cells, but they induce a like transformation in lymphoid cells that they come in contact with. In the next degree,

the conveyed cells exert a wider and more direct influence on the lymphatic parenchyma; by their angency the pattern of the primary tumour is carved out of the lymphatic gland. In the least intelligible class of cases, the influence is still more widely diffused and more direct, and is indeed invisible except in its effects. But it is as clearly derived from the primary tumour as in the former cases; for the lymphatic gland puts on the likeness of the primary tumour even to the most minute particulars. In this extreme form of infection no transport of entire cells can be traced; but we do not therefore seek for an explanation of the infection outside the properties of the cell. Virchow, in treating of purulent infection, was led to think that the infectiveness was inherent not in the cell-forms, but in the fluids that are present in or about the cells; and Billroth, in speaking of cancerous infection in the passage already quoted, thought that the infectiveness might reside in the "serum or intercellular substance."

A more general point remains to be noticed. In the growth of a secondary tumour, whether in a lymphatic gland or in an organ like the liver, there is not merely a resemblance between the individual tumour-cells of the secondary nodule and those of the primary tumour, but there is the most remarkable resemblance in the arrangement of the stroma and in the general conformation of the growth. The infection implies not only a transformation of the cells of an infected area into the likeness of cells of the primary tumour, but it implies also a consensus or co-operation among the elements of the infected part to assume the grouping and general plan of the primary tumour. Nothing can be more striking than to find that a lymphatic gland infected from a sarcoma growing from periosteum, acquires the appearance as if its own sarcomatous cells had grown interstitially within, or from the germinal surface of a periosteal tissue. Yet the mimicry of the infective process is as complete as that. The primary tumour, if it be in an epithelial organ, can be accounted for rationally by following out the functional aberrations of the organ, and if it grow from a tissue like periosteum, it can be rationally explained as a departure from the cellular laws of nutrition or of growth. The ultimate form of the primary tumour, one may say, is very much a matter of chance; its design is not predetermined, but it is developed step by step, and it may vary according to circumstances. But in the secondary

growth there is present from the beginning of the process a fully prepared design, which is followed as if implicitly. The primary tumour is the result of natural laws and their aberrations; but the secondary tumour is the result as if of a single creative fiat.

Thus, although the primary tumours of the breast are rationally to be considered as nothing else than diseased breasts or parts of the breast, which are still, to a certain extent, identical with or continuous with that organ of the body both structurally and functionally, yet from the point of view of their infectiveness, they manifest an autonomy or individuality which entitles them to be considered as separate existences. But that individuality is not for every tumour of the breast one and indivisible; or it should rather be said that a tumour of the breast is not always one and indivisible. It is a diseased process extending to more or less of the mammary structure; but the issue of the diseased process is not necessarily the same at all points where the process is in force. In the first of the group of four cases described above, there were two kinds of secondary structure found in two neighbouring lymphatic glands. One of these had the form of papillary outgrowths as if from the walls of acini, and the other resembled a collection of smaller acinous spaces lined with cubical epithelial cells with large nuclei. Corresponding differences were found in different parts of the diseased mammary tissue, as they are indeed constantly found in the various centres of disease in the widely-extended mamma of the bitch. Each of the centres can be a source of infection; and the case that has been referred to seems to show that such centres, existing quite close to one another, may each infect with its own type of structure different lymphatic glands lying in the same packet. That fact does not perhaps carry the analysis of the tumour-infective process much farther than it was before; but it is by the establishment of many such facts that we may hope in the end to analyse the process of tumour-infection, and to remove it from the region of mystery.

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